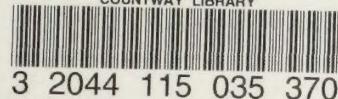
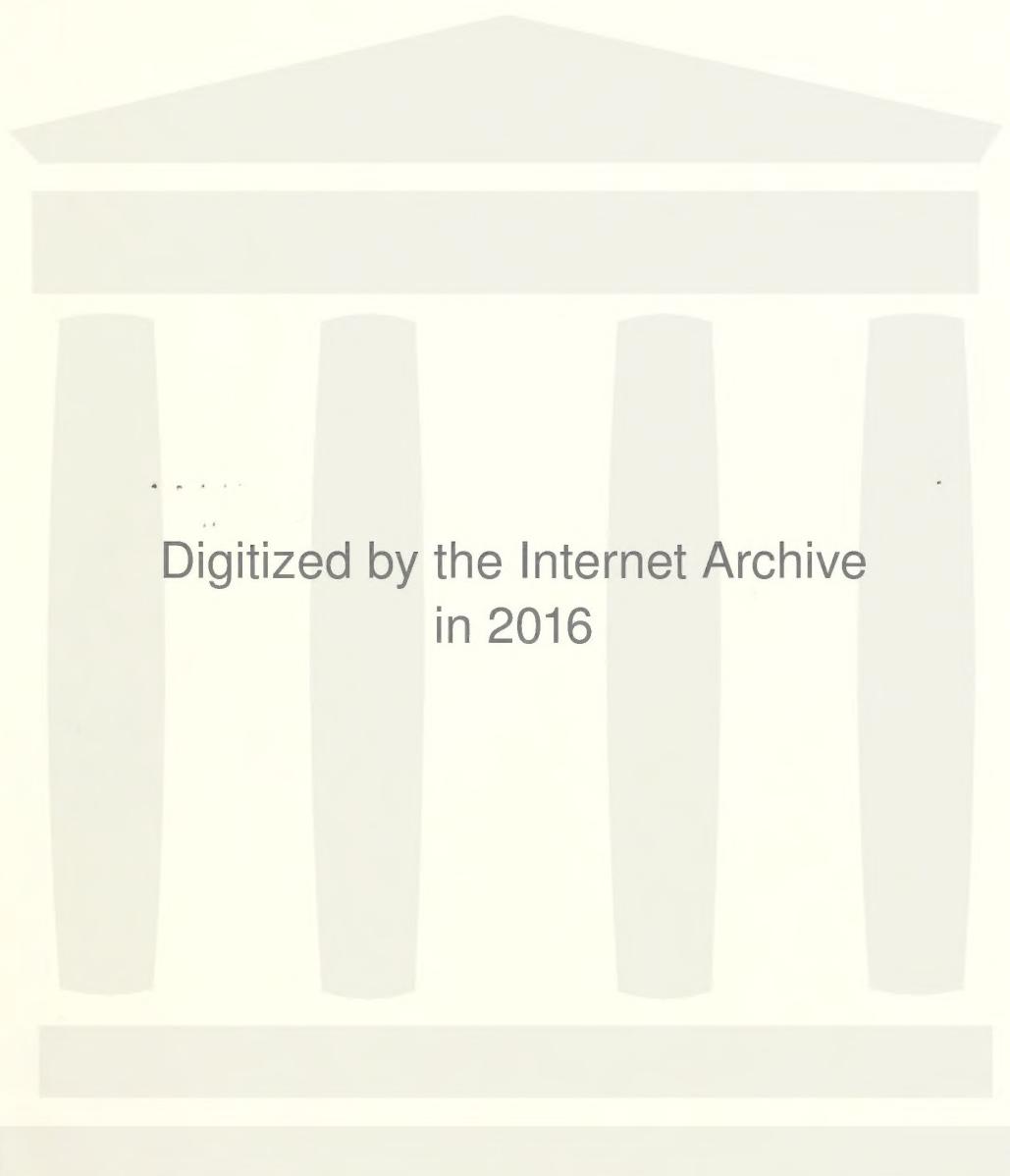


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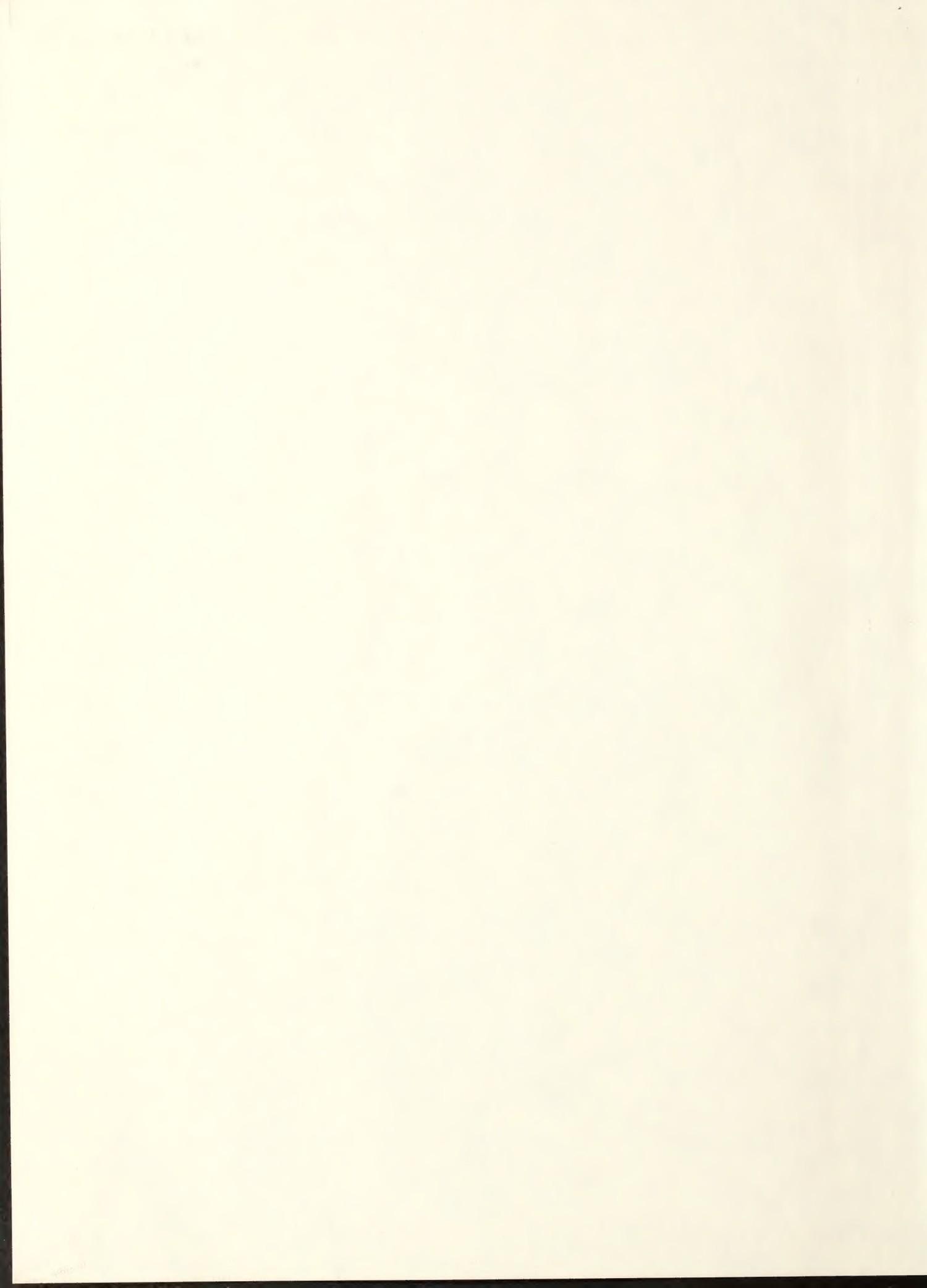
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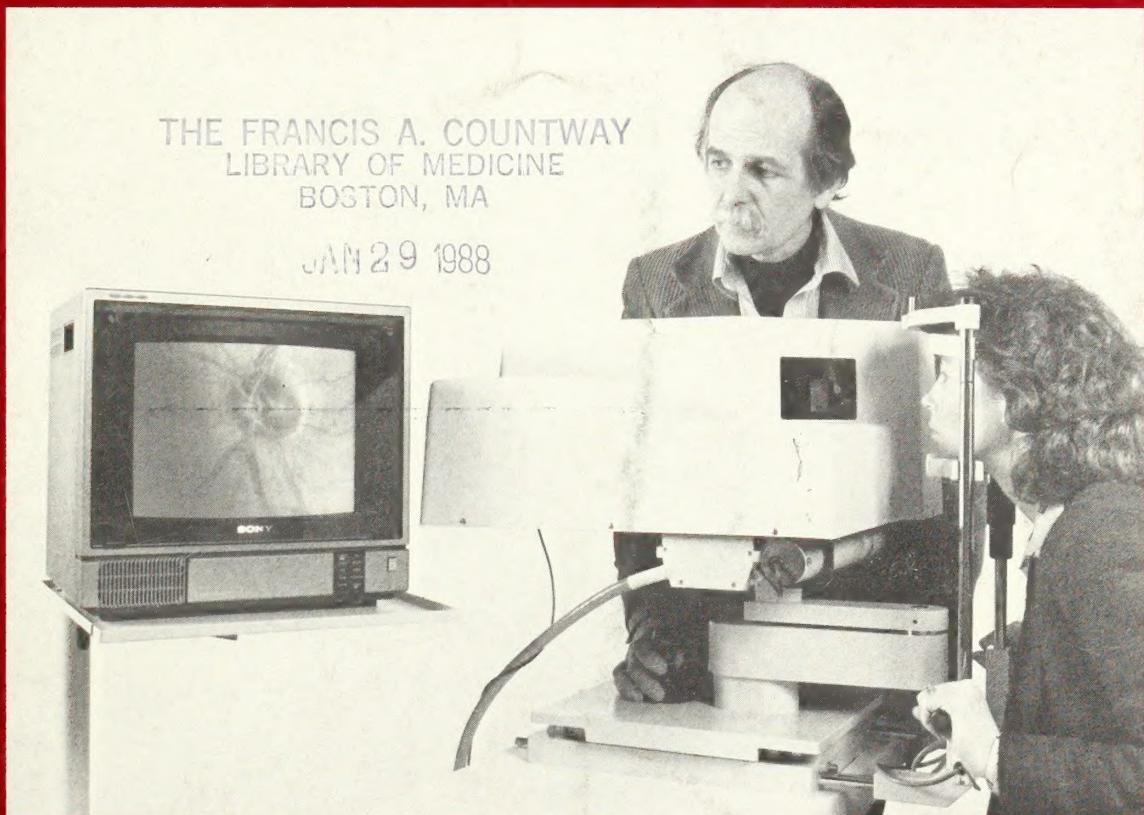


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January 1988

Volume 71, Number 1



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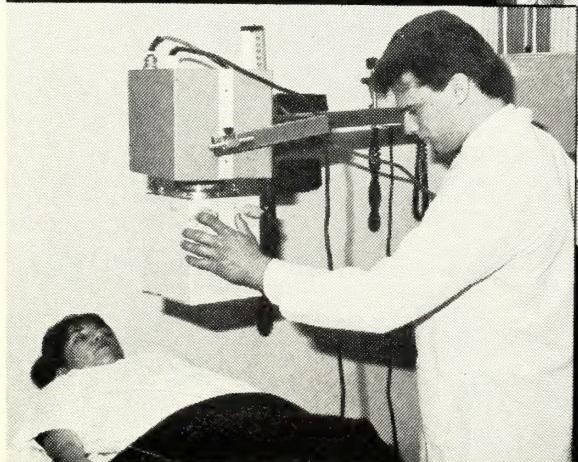
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Contraindications: There are no known contraindications to the use of Tagamet®.

Precautions: While a weak antidiuretic effect has been demonstrated in animals, Tagamet® has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity in humans.

In a 24-month toxicity study in rats at dose levels approximately 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving Tagamet®.

Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of Tagamet® HCl (brand of cimetidine hydrochloride) injection by intravenous bolus.

Symptomatic response to Tagamet® therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states have been reported on occasion, predominantly in severely ill patients.

Tagamet® has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when Tagamet® is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either Tagamet® 300 mg. q.i.d. or 800 mg. h.s. concomitantly with a 300 mg. b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.),

demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg. h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. [Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.]

Lack of experience to date precludes recommending Tagamet® for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken in patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: Diarrhea, dizziness, somnolence, headache, rash. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported. Reversible confusional states [e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation], predominantly in severely ill patients, have been reported. Gynecomastia and reversible impotence in patients with pathological hypersecretory disorders receiving Tagamet®, particularly in high doses, for at least 12 months, have been reported. Reversible alopecia has been reported very rarely. Decreased white blood cell counts in Tagamet®-treated patients [approximately 1 per 100,000 patients], including agranulocytosis [approximately 3 per million patients], have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia [approximately 3 per million patients] and a few cases of aplastic anemia have also been reported. Increased serum transaminase and creatinine, as well as rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including hypersensitivity vasculitis, have been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely.

likely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving Tagamet® has been reported.

How Supplied: Tablets: 200 mg. tablets in bottles of 100; 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 [intended for institutional use only]; 400 mg. tablets in bottles of 60 and Single Unit Packages of 100 [intended for institutional use only], and 800 mg. Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 [intended for institutional use only].

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Injection:

Vials: 300 mg./2 ml. in single-dose vials, in packages of 10 and 30, and in 8 ml. multiple-dose vials, in packages of 10 and 25.

Prefilled Syringes: 300 mg./2 ml. in single-dose prefilled disposable syringes.

Plastic Containers: 300 mg. in 50 ml. of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.

ADD-Vantage® Vials: 300 mg./2 ml. in single-dose ADD-Vantage® Vials, in packages of 25.

Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored at controlled room temperature. Brief exposure up to 40°C does not adversely affect the premixed product.

Tagamet® HCl (brand of cimetidine hydrochloride) injection premixed in single-dose plastic containers is manufactured for SK&F Lab Co. by Travenol Laboratories, Inc., Deerfield, IL 60015.

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WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or

without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin (ACTH)). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency.

Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine.

Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The

following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

BRS-DZ-L45

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Cover: Photograph of the Scanning Laser Ophthalmoscope courtesy of Thomas McInnes, Eye Research Institute of Retina Foundation, Boston, MA.

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It is rarely desirable to include a complete review of the literature in the references. An alphabetized bibliography is to be used only when the listing is of books suggested for supplementary reading.



BRIEF SUMMARY

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate.

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that the simultaneous administration of CARAFATE with tetracycline, phenytoin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. The clinical significance of these animal studies is yet to be defined.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of drug-related tumorigenicity was found in chronic oral toxicity studies of 24 months' duration conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies have not been conducted.

Pregnancy: Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients, adverse effects were reported in 121 (4.7%). Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED

CARAFATE (sucralfate) 1-gm pink tablets are supplied in bottles of 100 and in Unit Dose Identification Paks of 100. The tablets are embossed with MARION/1712. Issued 3/84

References:

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Choose CARAFATE® (sucralfate/Marion). Two recent studies show Carafate to be as effective in smokers as nonsmokers.^{3,4} A difference further illustrated in a 283-patient study comparing sucralfate to cimetidine⁵:

Ulcer healing rates:
(at four weeks of therapy)⁵

Sucralfate:

All patients	79.4%
Smokers	81.6%*
Cimetidine:	
All patients	76.3%
Smokers	62.5%

*Significantly greater than cimetidine smoker group ($P<.05$).

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EDITORIAL

Scanning Laser Ophthalmoscopy

The scanning laser ophthalmoscope (SLO) provides ophthalmologists with a new answer to an old question: How can we best see inside the eye? A product of American research and German technology, this new modality is now being tried out clinically at ten sites in the United States and Europe. Developed since 1978 by Robert H. Webb, PhD, Oleg Pomeranzett, Dipl. Eng., and George Hughes, Sc.D. at the Eye Research Institute (ERI) of the Retina Foundation of Boston, it has been licensed for production by G. Rodenstock Instrumente, GmbH, Munich, West Germany.

Traditionally, the retina has been visualized by dilating the pupil and viewing by means of an optical ophthalmoscope invented by Hermann von Helmholtz in 1851. Sufficient light is introduced to permit examination of the retina through a hand-held lens. The required bright light is a source of varying discomfort to the subject.

The SLO alters the process by *collecting* reflected light introduced through the pupil. The light source is a dim laser beam which moves in a scanning mode. The light intensity is only a fraction of that used in conventional ophthalmoscopes. As the laser beam scans the retina, it is collected by the SLO and transformed electronically into a television image so sharp that the pulse of retinal blood vessels can be visualized. In most cases it is not necessary to dilate the pupil.

With the retina displayed on a television screen, consultation and teaching are greatly facilitated.

There is no delay while fundus photographs are being developed. The retinal record is on video tape, permitting examination of the eye in motion. The dim light is much more comfortable for the *patient*, who can tolerate longer examinations. Since dilation of the pupil is not required, the procedure is greatly simplified. Further, the SLO promises to be a quick and effective means for routine eye examinations of large numbers of subjects.

The SLO provides further special capabilities. The laser beam can be modulated from bright to dim, or vice versa, very rapidly to form images. The image can then be projected onto the retina as onto a cinema screen. When asked if the image is visible, the patient's response permits the physician to correlate it with the specific position of the image. For the first time it will be possible to correlate response with a precise area of the retina, thus permitting the wrapping of scotomata. This unique potential of SLO has been under investigation at ERI since 1980.

The new technology has won widespread high praise and is recognized as a significant technological advance. As the equipment begins to appear in clinics and hospitals throughout the world, its great promise will be critically evaluated. It is but another example of why modern medicine is expensive.

Seebert J. Goldowsky, MD

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Sundial, newsletter of The Eye Research Institute of Retina Foundation, v. 13, no. 2, Fall 1987.

Thalidomide and D.E.S. (They could happen again.)

Sometimes even the most promising drug may have unexpectedly adverse reactions in patients. Pre-market testing identifies most toxic drugs before release for patient-care use, but not all. Toxicity in some drugs can only be determined through adverse reactions detected among a larger number of patients over a longer period of time.

The plain truth is that a patient's health may be at risk. Adverse drug reactions cause death in approximately 30,000 patients annually in the United States alone. So, if you suspect an adverse drug reaction, please report it promptly. We may all live longer because you did.



The Adverse Drug Reaction Reporting Project

of the Rhode Island Department of Health

To report an ADR by phone, call **456-ADRS** weekdays between 9 and 5. To receive mailing forms and additional information, call the Health Department at 277-2901.

Rhode Island Women's Awareness of Breast Cancer Detection Techniques: Implications for the Rhode Island Clinician

Mammography in Rhode Island Is Vastly Underutilized

Francis H. Scola, MD
Barbara Schepps, MD
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John Cronan, MD

Breast cancer is the number two killer of women in the United States, second only to lung cancer. It accounts for 26 per cent of all cancers in women. Nationally, approximately 41,000 women will die from breast cancer during this year, and ap-

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proximately 250 will be Rhode Islanders. It is estimated that more than one-half million American women have undiagnosed breast cancer that could be detected by a carefully performed mammogram. If these cases were diagnosed and treated, 15,000 lives could be saved. Survival rates would be even higher if mammography were combined with monthly breast self-examination and an annual physical examination.^{1, 2}

During the 1960s evidence from the Health Insurance Plan of Greater New York demonstrated that early detection of breast cancer through the use of mammography and physical examination resulted in a 38.1 per cent reduction in the breast-cancer death rate.² The Breast Cancer Detection Demonstration project, which commenced in 1973, demonstrated that mammography was the oldest breast-cancer screening tool with survival benefit for asymptomatic women over the age of 50.³ More recent evidence has also shown that mammography can detect very small localized breast cancers in women aged 35-49, which suggests the possibility of better survival in this group as well. Despite improvements in methods for diagnosis, it is surprising that the death rate from breast cancer increased from 22.2 to 22.8 deaths per 100,000 during the years 1950 to 1984.⁴

The American Cancer Society's most recent (1984) guidelines for screening asymptomatic women for breast cancer are as follows:^{5, 6}

1. Women 20 years old and over should practice breast self-examination.
2. Women 35 to 40 years of age should obtain a baseline mammogram.
3. Women 40 to 50 years of age should have annual or biannual mammography based upon physical findings and risk factors.
4. Women over 50 should have an annual mammogram.

Compliance with these recommendations is believed to be fairly low. In a household survey of 540 women aged 18 and over, only 15 per cent had ever had a mammogram.⁷ A study of women in England also showed low participation rates: of 2000 women aged 45-64 only 20 per cent had ever had a breast examination or mammography or both.⁸ Older women in particular have been shown to have poor knowledge of breast cancer screening techniques.^{9, 10}

Rhode Island women's awareness of breast cancer detection techniques has not as yet been documented. With this in mind, the Department of Diagnostic Radiology at Rhode Island Hospital undertook a survey to examine awareness of the risk of breast cancer among Rhode Island women, and to estimate the proportion of Rhode Island women who have utilized mammography or discussed its use with their physicians.

Methods

During June of 1986 a telephone interview was conducted among a random sample of 235 Rhode Island women aged 21 and over having telephone service. The initial sampling frame consisted of all listed Rhode Island telephone numbers. After random selection, a double-digit random replacement approach was applied to the last two digits of the phone number to allow inclusion of unlisted telephone numbers. Business telephone numbers were excluded from the sample, and up to three call-backs were made to reduce the probability of non-response error. The non-response rate for eligibility households (those with a female household member over the age of 21) was approximately thirty per cent. Individuals who did not speak English were excluded from participation.

Results

Characteristics of the Sample. A total of 235 women participated in the telephone survey. The distribution of the sample by age is presented in Table

I. The age distribution of the sample differs somewhat from estimates based upon census data.¹¹ The sample proportions in the youngest age groups are very similar to the proportions reported in 1980 census data, but the older age groups are underrepresented. This difference is most apparent for those over 70, and may be partially explained by the inability of a telephone survey of households to reach institutionalized elders, and by the presence of elders in relatives' households.

Table 1. Sample Description: Survey of Rhode Island Women, aged 21 and over (n=235), June 1986

Age	n	Sample %	% of R.I. women aged 20 and over (US Census)
Under 40	117	49.8	41.3
Forties	29	12.3	13.0
Fifties	31	13.2	16.1
Sixties	40	17.0	14.3
Seventy or over	18	7.7	15.3

Awareness of Breast Cancer as a Leading Cause of Death. Results related to awareness of breast cancer as a leading cause of death among women are presented in Table 2. Women in their forties were most aware of breast cancer as a leading cause of death, and women in their fifties and sixties were least aware. The proportion of women in their forties who mentioned breast cancer was significantly different from the proportion of those under forty who mentioned it, and this proportion was also significantly higher than the corresponding proportion for older women (50 or over).

Table 2. Awareness of Breast Cancer as a Leading Cause of Death by Age

Age	% Mentioned Breast Cancer	% Refused
Under forty	47.9	5.1
Forties	72.4	0.0
Fifties	38.7	0.0
Sixties	45.0	2.5
Seventies and over	50.0	0.0
Total	49.4	3.0

Awareness of Breast Cancer Detection Techniques. Results of analyses related to awareness of breast cancer detection techniques are presented in Table 3. The sample surveyed was most aware of self-examination as a method for detecting breast

Table 3. Awareness of Breast Cancer Detection Techniques

Detection Technique	% Mentioned (n)	95% C.I.
<i>Mammography</i>		
Under 40	46.2 (54)	
Forties	55.2 (16)	
Fifties	54.8 (17)	
Sixties	42.5 (17)	
Seventy +	33.3 (6)	
Total	46.8 (110)	40.5-53.1
<i>Self Exam</i>		
Under 40	67.5 (79)	
Forties	72.4 (21)	
Fifties	61.3 (19)	
Sixties	57.5 (23)	
Seventies +	55.6 (10)	
Total	64.7 (152)	58.7-70.7
<i>Exam by Physician</i>		
Under 40	31.6 (37)	
Forties	34.5 (10)	
Fifties	51.6 (16)	
Sixties	25.0 (10)	
Seventy +	38.9 (7)	
Total	34.0 (80)	28.0-40.0

cancer, followed by mammography, and lastly examination by a physician. Very few individuals were unable to mention a method for detecting breast cancer (.4 per cent). Awareness of breast cancer detection techniques consistently peaked among women in their forties and fifties. Fifty-five per cent of women in these age groups mentioned mammography as a method of detection, 67 per cent mentioned self-examination as a method of detection, while 43 per cent mentioned examination by a physician.

Statistical analyses by age category revealed that awareness of some breast cancer detection techniques was related to age. The proportion of 40 to 59 year old women who were aware of mammography was significantly different from the proportion of women aged 60 and over who were aware of mammography ($p = .04$, one-tailed test). Similarly, awareness of examination by a physician as a technique for detecting breast cancer was significantly different between those aged 40 to 59 and those aged 60 and above. Awareness of self-examination was not significantly different between these two age groups, although a relatively large proportion of women in their forties mentioned this method of detecting breast cancer. Although statistically significant differences between older and younger women were not observed for all detection techniques, the same pattern was observed: for all three detection techniques, awareness was highest for women

aged 40 to 59, women under 40 were only slightly less aware, and the oldest women (60 and over) were the least aware.

Experience with Mammography. Results from questions dealing with experience with mammography are presented in Table 4. Women aged 60 and over were the most likely to have discussed mammography with a physician, and those under forty were the least likely to have done so. Chi-square analysis revealed that a report of ever having discussed having a mammogram with a physician was significantly related to age ($X^2 = 8.922$, $p = .012$, $df = 2$).

Twenty-two per cent of women surveyed responded "yes" when asked if they had ever had a mammogram. This proportion differed by age: those under 40 were the least likely to report having had a mammogram, whereas those aged 40-59 and 60 and over reported similar experience with mammography. The chi-square statistic for the association of age and report of ever having had a mammogram was significant ($X^2 = 26.0$, $p \leq .001$, $df = 2$).

When asked about the likelihood of having a mammogram within the next 12 months, 14 per cent responded that a mammogram was likely. Those under forty were the least likely to report plans for a mammogram in the next year, and the most likely to be unsure. Those aged 40-59 and 60 and over had very similar proportions who reported that a mammogram was likely. The association of age and likelihood of a mammogram during the next 12 months was significant. ($X^2 = 13.42$, $p = .009$, $df = 4$).

Table 4. Proportion of Sample Reporting Experience with Mammography

	% yes	(n)	95% C.I.
<i>Discussed mammography with physician</i>			
Under forty	22.2	(26)	
40-59	35.0	(21)	
60 and over	43.1	(25)	
Total	30.6		24.6-36.6
<i>Ever had a mammogram</i>			
Under 40	8.5	(10)	
40-59	33.3	(20)	
60 and over	37.9	(22)	
Total	22.1		16.8-27.4
<i>Mammogram within next 12 mos. likely</i>			
Under 40	9.4	(11)	
40-59	18.3	(11)	
60 and over	19.0	(11)	
Total	14.0		10.0-18.0

Discussion

Results of this survey indicate that under 50 per cent of Rhode Island women sampled knew that breast cancer was one of the leading causes of death among women or that mammography was a method of detecting breast cancer. Awareness of breast cancer as a leading cause of death, and awareness of mammography and examination by a physician as detection techniques were significantly lower among older women (60 and over) than among those aged 40 to 59. The same trend was evident for self-examination; however, a significant difference was not observed. These results are consistent with reports in the literature which document inadequate awareness of breast-cancer detection techniques by older women in other populations.

The proportion of women reporting having had a mammogram is fairly small: In the group aged 40 and over, only 36 per cent responded that they had ever had a mammogram. Because of selective recall, this proportion may be an underestimate of the true proportion of women who actually have had a mammogram. However, given that ideally 100 per cent of women aged 40 and over should have had a baseline mammogram, a proportion this low indicates a wide gap between public health goals and Rhode Island population-based estimates.

Age was significantly related to report of ever having had a mammogram and likelihood of having a mammogram within the next 12 months. Thus, even though older women are less likely to be aware than younger women of breast cancer and breast cancer detection techniques, their behavior is different. They are more likely to have had experience with mammography, and to foresee future mammography. This discrepancy between awareness and practice suggests that, especially for the older women, the impetus for having a mammogram may not come from the woman herself. It suggests a crucial role for the primary-care physician in influencing breast-cancer prevention practices. In contrast to the situation for older women, the relatively high awareness of breast cancer detection techniques by women in the age group 40-59 is sharply contrasted by their low rates of reported mammography. This discrepancy also underscores the crucial role of the primary-care physician in referral for mammography, and suggests that there is a large pool of women aged 40-59 who, although aware of breast cancer detection techniques, are not being referred for mammography.

While the role of the primary-care physician in referral for mammography is believed to be crucial for mammography practice, only 39 per cent of women over 40 reported discussing mammography with their physician. Again, even after considering the likelihood that this statistic underestimates the true population proportion as a result of inability to recall information, it suggests low rates of participation in breast-cancer screening by primary care physicians in Rhode Island.

Other research has shown that it is not a common practice for physicians to recommend mammography as a primary prevention measure.^{7, 12, 13} In a recent survey the American Cancer Society found that only 11 per cent of primary care physicians were referring their patients for mammography as specified by American Cancer Society guidelines (baseline mammography between 35 and 40, a mammogram every other year until age 50, and yearly thereafter).^{5, 6, 14} Reasons given by primary care physicians for nonreferral included are: 1) high cost of examination, 2) fears of radiation exposure, 3) doubts about the effectiveness of mammography.¹⁴

Recent developments and research indicate that these concerns are generally untenable.¹⁵⁻²² Due to high-volume and low-physician input, the cost of mammography now approaches \$50, and with new film-screen techniques the absorbed radiation dose has been greatly reduced. In 1972 a study originating from the National Academy of Science²³ reported that 1 rad of absorbed radiation to the midline tissue of the breast would increase the risk of breast cancer by 1 per cent to yield a total risk of 7.07 per cent. Thus, a 50-year-old woman getting a mammogram with a midline exposure of 1 rad every year for 20 years would increase her theoretical risk from 7 to 8.4 per cent. At the present time with improved film-screen techniques, the absorbed dose has been reduced to less than 40 millirads. The effectiveness of mammography has been demonstrated in the first Breast Cancer Detection Demonstration Projects.³ These data show that 47 per cent of early breast cancers were detected by mammography alone, whereas only 9 per cent of cancers were detected by physical examination alone. Ten years later, 90 per cent of all breast cancers are still detected by the patient first.¹ In this group, 50 per cent have metastases to axillary nodes or other parts of the body and a five-year survival rate of only 60 per cent. Yet, a tumor detected by mammography that is less than 1

centimeter has no metastasis and a 10-year survival rate of 95 per cent. These findings underscore the value of mammography in picking up early cancers with vastly improved survival rates. Results of our survey show that, although there is a relatively high awareness of breast-cancer detection techniques by women, mammography in Rhode Island is still a vastly underutilized tool in the early detection of breast cancer.

Recommendations

Mortality from breast cancer has not been significantly reduced within the last 40 years of recorded statistical records, despite the effectiveness of mammography in detecting breast cancer in its earliest stages.²³ Improved awareness of the extreme benefits of regular mammograms is necessary for women aged 35 and over, and for referring physicians. At the national level the American Cancer Society and the American College of Radiology have begun educational campaigns through television, radio, and print advertisements. Locally, a pilot screening project has been instituted at Rhode Island Hospital. The resultant publicity may increase Rhode Island women's and physicians' awareness of the benefits of mammography, but concentrated health education is also necessary, especially for women aged 35 to 40 who are in need of a baseline mammogram.

This research indicates that there is a large discrepancy between American Cancer Society recommendations for breast cancer prevention practices and Rhode Island women's reported practice. As reported for other populations, awareness of breast cancer detection techniques is particularly low among women over age 60. However, even among the group of women who are most aware of breast cancer detection techniques (those aged 40 to 59), the proportion of those who have had a mammogram, who are planning to have a mammogram, and who report having discussed mammography with a physician is small.

A crucial question affecting utilization of mammography is: Can physician compliance with American Cancer Society guidelines be improved? The literature suggests that the answer to this question is yes. A randomized clinical trial designed to assess the effectiveness of a program whose purpose was to increase outpatient medical clinic staff compliance with preventive medical guidelines provides supportive evidence. Age-specific checklists of all recommended prevention procedures were attached to each patient's

chart, and weekly seminars dealing with screening issues resulted in mammography and immunization rates that were significantly higher in participating clinics than in control clinics.²⁴ Evidence such as this indicates that dramatic improvements in the prevalence of prevention practices can be achieved quickly, and with relatively simple procedures.

The task is tremendous. There are over two-hundred-thousand women in Rhode Island over the age of 35,¹¹ and one in ten of these women is likely to develop breast cancer during their lifetime. Despite advancing knowledge and improved technical ability in early detection and methods of treatment, these figures have changed little in the past few decades. Only through improved public and professional awareness of the effectiveness of mammography and concentrated efforts by physicians toward compliance with American Cancer Society guidelines will the potential for decreased breast cancer mortality be realized.

Acknowledgements

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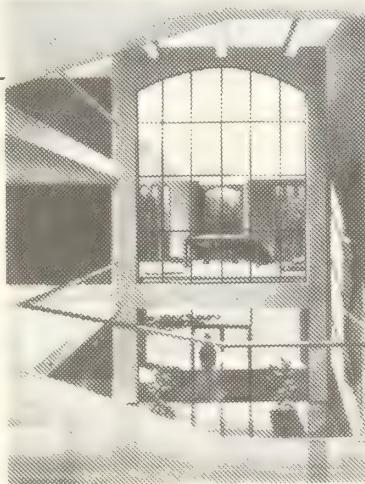
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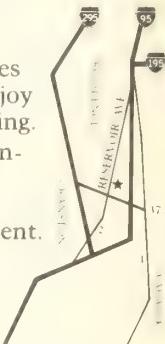
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- 11 Rhode Island Medical Center, "Topics in Epidemiology and Neurology," Stanley M. Aronson, MD, Brown University Medical Program, 464-3456
- 14 Institute of Mental Health, Case Conference, Max Faintych, MD, presenting, Barry Fogel, MD, moderating, Sponsor — Medical Education Committee, 464-1670
- 18 The Woonsocket Hospital, "Drug Monitoring in the Geriatric Patient," Darrell R. Abernathy, MD, PhD, Sponsor — Marion Laboratories, Inc., 767-3211, ext. 2310
- 19 Rhode Island Medical Center, "Clinical Rounds — Psychogeriatrics," Barry S. Fogel, MD, Director — Psychiatric Medical Program, 464-3456
- 21 Rhode Island Medical Center, "Clinico-Pathologic Conference," Invited Discussors and Pathology Staff, 464-3456
- 28 Institute of Mental Health, Case Conference, Saul Martin, MD, presenting, Eileen McNamara, MD, moderating, Sponsor — Medical Education Committee, 464-1670
- 29-30 Brown University Program in Medicine, New England Pharmacologists Annual Meeting, 863-3115

FEBRUARY

- 8 Rhode Island Medical Center, "Topics in Epidemiology and Neurology," Stanley M. Aronson, MD, Brown University Medical Program, 464-3456
- 11 Institute of Mental Health, Case Conference, John Melchionna, MD, presenting, Leah Cullen, MD, moderating, Sponsor — Medical Education Committee, 464-1670
- 16 Rhode Island Medical Center, "Clinical Rounds — Psychogeriatrics," Barry S. Fogel, MD, Director — Psychiatric Medical Program, 464-3456
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- 25 Institute of Mental Health, Case Conference, Sarah Zamari, MD, presenting, David Kroessler, MD, moderating, Sponsor — Medical Education Committee, 464-1670
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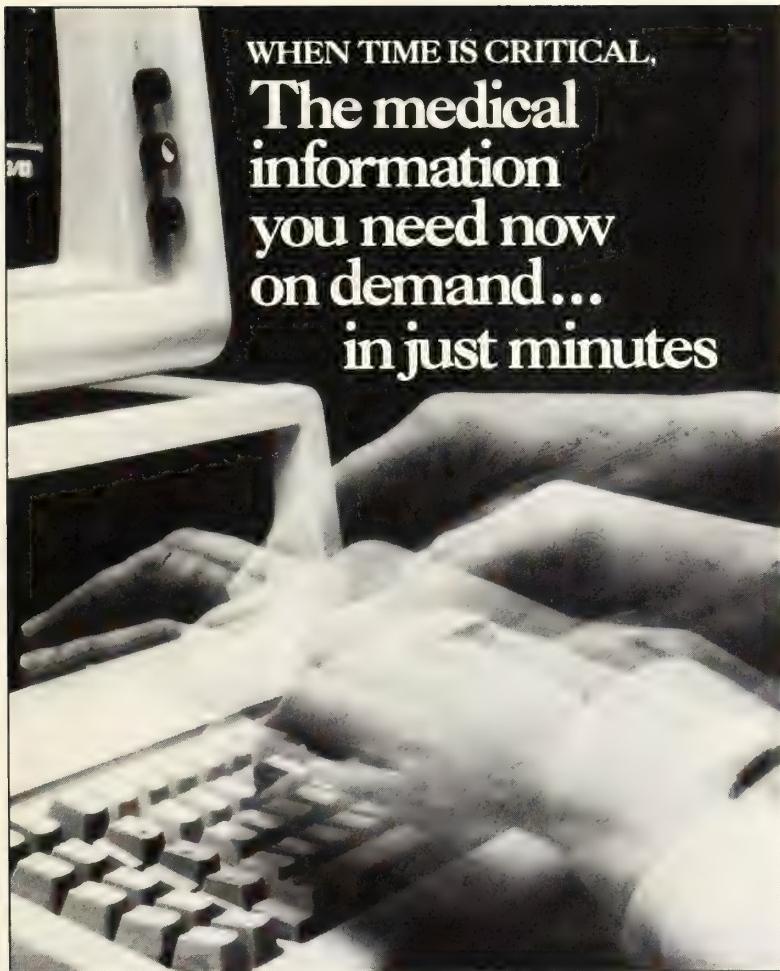
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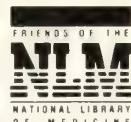


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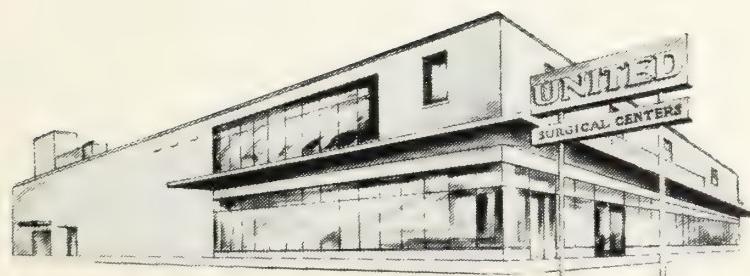
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The Pawtucket Heart Health Program

III. Social Marketing To Promote Community Health

R. Craig Lefebvre, PhD
Elizabeth A. Harden, BA
Barbara Zompa, BA

Events of the past several years have signalled a shift in chronic disease epidemiologic methods from those focused on description and explanation to ones that target change in established risk factors and their morbid and mortal sequelae. These changes have been stimulated, in part by the successful reports of the North Karelia

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Supported in part by Grant HL23629 from The National Heart, Lung and Blood Institute, United States, Department of Health and Human Services.

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Project¹ and the Stanford Three-City Study²; the three federally-funded community research and demonstration studies for cardiovascular disease prevention in California,³ Minnesota,⁴ and Rhode Island⁵; and numerous other national and local community initiatives. All of these efforts have gained support from a growing consensus among public health scientists and policy-makers that broad-based interventions (versus those that target only individuals identified as "high-risk") are more likely significantly to alter the risk status of the population and improve the public health — especially in relation to cardiovascular diseases.⁶⁻⁸

The shift from passive observation to active intervention on risk behaviors (eg, cigarette smoking, consumption of foods high in saturated fat and sodium, sedentary living) has brought with it a search for methods that can reach and influence large numbers of people. Techniques used by the Pawtucket Heart Health Program (PHHP) include print, radio and televised messages; small group behavior change programs delivered by trained lay volunteers; community and worksite-based blood pressure, blood cholesterol and multiple risk-factor screening, counseling and referral events (SCOREs); self-help programs; school curricula; smoking prevention programs; risk-behavior change competitions (eg, the "Quit and Win" smoking cessation contest and the "Lighten Up" weight loss challenge); and environmental programs such as shelf-labeling in grocery stores and menu-labeling in restaurants to indicate low sodium and low fat foods.

The theoretical underpinnings of the PHHP intervention have been described elsewhere.^{9, 10} Briefly, a community activation model that involves lay volunteers in program delivery is the cornerstone of this approach. Elements of community organization theory, social learning theory, and behavioral community psychology are blended to fashion risk-behavior change programs that target cross-sections of the community (eg, individuals, groups, organizations) across various phases of the learning process (ie, motivation, skills training, and maintenance). However, as one moves from programs designed to change individuals to ones designed to alter the health status of communities, we are finding that concepts and techniques of social marketing form a useful vantage point from which to identify, analyze, and intervene on risk behaviors. The literature on social marketing is growing rapidly, and several papers and books are recommended to the interested reader.¹¹⁻¹⁶ In this context, the many intervention programs of the PHHP can be viewed as "products" that other community groups may wish to market to their own constituencies. However, it is clear that an encompassing theory of risk behavior intervention is necessary by which to design and implement these programs. PHHP has adopted a model based on social marketing that includes broad-based efforts by health professionals to influence the awareness, knowledge, or behavior, or combinations thereof, of large numbers of people. The careful and strategic use of social marketing to formulate, carry out, and evaluate new public health innovations—whether they be group programs, SCOREs, competitions, or others,—can help maximize the delivery and impact of health promotion/disease prevention programs in the community. Market planning includes adequate market research on the specific problem(s) to be addressed—including the setting of objectives; analysis of the community including segmentation by sociodemographic, geographic, or psychographic variable, or combinations thereof, analysis of distribution channels; and the development of a marketing strategy for the various products. With respect to the implementation process, social marketing differs little from what one encounters in consumer marketing. What is different is that social marketing often involves promoting intangible (eg, a healthier life) or remote outcomes (eg, a longer life) to persons not necessarily interested in the product, whereas consumer marketing can more easily focus on immediate, tangible outcomes (eg, fresh breath,

satiety, self-satisfaction).

The principles of social marketing presented in this paper guide many of the PHHP community-based activities. However, it is also important to note that physicians are also "selling health"—whether it be by proposing surgical procedures, encouraging medication compliance, or providing health guidance to an organization or a community. Indeed, many of the marketing and communication strategies described here are directly relevant to the Rhode Island physician community and their efforts to promote the health and well-being of their patients.

This is the third of a series of five papers describing the structure and goals of The Pawtucket Heart Health Program. The first two papers appear in the December 1987 issue of the JOURNAL and the fourth paper follows in this issue. The fifth paper will appear in a subsequent issue.

A social marketing approach to public health intervention involves seven major features: a message, a source, a target audience, communication channels, timing, evaluation methods and feedback mechanisms. The last two components are critical elements for an agency that is planning to conduct marketing campaigns. Without adequate evaluation of the campaign's effect on the desired outcome (eg, increased knowledge about cardiovascular disease (CVD) risk; more people attending blood cholesterol SCOREs), there is little justification for undertaking the project. Further, feedback both to the cooperating agencies and the target groups is essential not only to reinforce their participation in the campaign, but to facilitate access to them for subsequent campaigns. The evaluation methods that are available to health agencies are numerous, and examples of the PHHP evaluations systems are detailed elsewhere in this issue.¹⁷ However, the bare minimum of data should include an accurate enumeration of participants (or contacts) reached by the campaign and basic sociodemographic information (ie, breakdowns by age and gender). Given the goals of the campaign, other information might also be obtained. For instance, Lefebvre et al¹⁸ reported both initial blood cholesterol levels of SCORE participants and the two-month changes for the approximately two-thirds of them that had returned for follow-up. This information was used for internal program planning and shared with cooperating agencies and

worksites. In addition, two news releases also appeared in the local paper — one noting that 60 per cent of the population who were screened were above recommended goal levels and another reporting that large numbers of these same individuals were successful in lowering their blood cholesterol through prudent dietary changes.

The planning of a social marketing campaign itself involves a careful blending of the other five elements. Timing forms the context within which to structure the campaign. Interventions can capitalize on time (eg, tagging a local smoking campaign onto national "Great American Smoke Out" promotion efforts) or be undermined by a misuse of it (eg, weight loss campaigns during the holiday season). Given proper timing, the other four components influence each other so that, as seen below, the selection of the sources of the message, the communication channels, and the nature of the message itself will complement each other in the final version of the campaign.

There was obviously a number of permutations that evolve from the structuring of these four elements — message, source, channel, and audience. Indeed, while one usually begins campaign planning with a "message," it is common in the planning of the campaign for the "audience" element to command the most attention (eg, young women, men over 40). However, specific attention just to one or two elements in our experience produces less-than-optimal strategies and results. To achieve the desired impact of community health promotion, careful consideration of all four elements in campaign planning is essential.

The goals of the campaign must be embodied in the message, or messages, that one is trying to bring to the target audience. Message design and construction is considered by some practitioners to be the hallmark of social marketing; great ideas, poorly expressed, often lead to little change in awareness, knowledge, or behavior among the target audience.

Effective message design rests on a strong concept platform. This platform should help guide the creative process and provide the basis for the wording of the promotional, educational messages, or both. For each message, three concerns must be addressed in the concept platform:

- Benefit: (1) Noting the *importance* of the topic to the target audience; (2) making the benefit of interest to that audience, and (3) addressing the audience's difficulty in *identifying* or recognizing the benefits. Often, health professionals fail to recognize that the lay audiences to whom they

are directing messages have little appreciation or understanding of many of the benefits of health practices.

- Support: (1) Providing factual *information* that may form the basis for decision-making and action; and (2) attending the *contextual cues* of the message such as the tone, models, setting, lighting, music, and "sex appeal" to enhance and support the factual information. What often discriminates health messages from more commercialized communications is overemphasis of the former on factual presentation with little attention to the context of that presentation. In turn, many health messages are poorly attended to, remembered, and acted upon by the target group.

- Action: (1) *Specifying* steps that can be implemented immediately by the audience; or (2) outlining *interim steps* they can use (calling a telephone number, writing to an address, or seeing an intermediary person such as their physician for more information). All too often we see messages that totally neglect this most important aspect of the communication process — provision of easy steps for the target group to take in positive response to the message.

Once the concept platform has been arrived at, message design can begin in earnest. Whether one is involved in producing promotional flyers, articles for a newspaper column, television public service announcements and shows, school curricula, or community awareness and behavior change campaigns, elements of message design should be attended to at all phases of production. Manoff outlines the four major factors of design strategy as (1) content, (2) design, (3) persuasion, and (4) memorability.¹⁴

Content factors are intended to state a *problem* for the *target audience* in such a manner that it addresses actual or anticipated *resistance points* to the message by the target audience. The content should also provide a solution that depends on the message recipient carrying out *expected actions* that have credibility to him/her because of the *authoritative source* to which they are ascribed. In sum, the content factors recapitulate the essential elements of the social marketing campaign concepts in images and sounds that will strike a responsive cord with the target audience.

Design factors which have been found to influence the effectiveness of a message include the notion that the expression of a *single idea* in a radio spot, pamphlet, poster, or brochure is preferable to multiple messages. Presentations should also be *linguistically and culturally relevant* to the target group as well as providing *situation and*

character identification opportunities. Incorporating a distinctive message style that has a *low fatigue index* will help ward off disinterest and boredom after repeated exposures to the message.

Message design strategy should keep in mind that messages must persuade people to feel, think, or act differently than they did before. Manoff identifies a variety of factors that can enhance the "persuasion index" of a message, including: offering *reasons why* the message is being proposed and desirable to the target group, demonstrating *empathy* with the audience, *arousing concern* in the audience about the problem, providing compatible and feasible *action capabilities* to the audience in response to the message, monitoring the *believability* of the message so that it does not oversell the audience, *creativity* that does not detract from the concept strategy itself, and promoting *benefits* for the new behavior as an incentive to try it.

The fourth factor, memorability, is facilitated when *idea reinforcement*, different modalities converging on the same idea, occurs either within a message or among a series of messages: *Distractions are minimized* so that the receiver's focus is on the message — not the medium conveying it; and *repetition* of key message elements occurs within or among similar messages.

In the production of the multiple promotions, products, services, and campaigns that are the PHHP, these ideas have provided a framework from which to approach the changing of the public's behavior and to structure intervention activities. Many lessons have been learned from our experiences and many more are undoubtedly to be learned. Yet, the problems and challenges faced by people like ourselves, who undertake efforts such as these, whether on a larger or smaller scale, will more likely find solutions when they are approached as a social marketing opportunity.

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The Pawtucket Heart Health Program

IV. Community Level Programming For Heart Health

Thomas M. Lasater, PhD

R. Craig Lefebvre, PhD

Richard A. Carleton, MD

The incidence of many chronic diseases is related to personal, culturally supported behavior such as dietary choices, smoking choices, and safety choices.

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Comprehensive community level health promotion programming requires components targeting each of the major aspects of the behavior change process including increasing readiness for health promotive behavior, teaching of the actual skills required to make changes in or to prevent adoption of risky behavior, and finally components designed to maintain healthy behavior. In addition to targeting various aspects of behavior change, it is also important that there be program components directed at the various social-cultural levels that make up a community — individuals, small groups, organizations, and the total community. Such a multileveled approach can reach all strata of the community.

In order to illustrate this approach as applied by the Pawtucket Heart Health Program (PHHP), the balance of the current paper will present a description of many of the program elements that, taken together, comprise the cholesterol reduction program of the PHHP.

There are four basic approaches to population-wide cholesterol reduction. These include measurement of an individual's cholesterol level, advising changes in eating patterns with respect to saturated fats and dietary cholesterol intake, loss of excess body weight, and referral to the medical care system for indicated drug therapy.

An important class of materials for comprehensive programming includes those broadly termed self-help materials, such as single sheets of material based on a single theme (eg, dining out, dairy products, selecting and preparing meat). These "tip sheets" can be used in a number of formats such as posters, payroll stuffers, handouts, and mailouts. We also have self-help kits. Each is essentially a behavior change program designed to be used at home with a few simple steps. These include a Nutrition Kit and a Weight Loss Kit. Another popular self-help type of material has been the cookbooks and recipe cards compiled from recipes submitted by citizens of the city in response to recipe contests and heart healthy "cook-offs."

Programs for small groups are traditional and often effective means of helping behavior change. Relevant to cholesterol change, PHHP has small group programs on weight loss and heart healthy nutrition. These groups generally meet an hour a week for eight to ten weeks. Each is designed to be led by volunteers who have been trained and certified by PHHP staff. These are state-of-the-art behavior change programs with demonstrated efficacy.¹

A major cornerstone of our programming are cholesterol and weight loss SCOREs (screening, counseling, and referral events). This is a highly mobile service, visiting all regions of the city. Each involves an assessment of the target risk factor such as cholesterol or weight, followed by an immediate counseling session, provision of self-help materials, and urging of the individual to obtain a follow-up measure of the risk factor following behavior change attempts. Participants are referred to physicians for cholesterol levels above the National Cholesterol Consensus Conference High Risk values.² For cholesterol, SCOREs include the use of the new fingerstick methodology represented by the Kodak model DT60 and Boehringer Mannheim Reflotron model clinical chemistry analyses. These allow total cholesterol to be assessed from a fingerstick blood sample in three to five minutes. Over 10,000 citizens have taken advantage of PHHP's cholesterol SCORE,

and over 20,000 field assessments have been conducted since acquiring the equipment several years ago. In addition to the mobile SCORE functions, PHHP has established several stationary walk-in sites for our SCOREs as well. One example of a walk-in SCORE site which also dispenses a full range of heart healthy materials is our storefront resource center called The Main Artery on Main Street in Pawtucket.

The Main Artery offers heart health help to all patients in Rhode Island. This includes a wide range of nutrition and other behavior change materials, all of which have been carefully screened by professional staff for safety and efficacy. In addition to the materials, inexpensive assessment of blood pressure, cholesterol, and weight with accompanying counseling, referral as needed, and self-help materials are available.

Another major resource in comprehensive programming is the use of the media. For reasons of experimental design as well as cost, PHHP has not utilized commercial television or radio. Cable television with its free public access is used for program announcements, cooking demonstrations, and airing of attractive behavior-change programs.

PHHP has also made extensive use of print media. A regular column is written by PHHP staff for the local newspaper to inform, motivate, teach, reinforce volunteers assisting the PHHP effort, and promote upcoming events. The staff have also become knowledgeable about the kinds of feature stories that appeal to newspapers and continually feed such ideas to them. Sometimes PHHP or its volunteers write the feature story while at other times news reporters will follow up on a lead given them. Human-interest stories are particularly effective in helping citizens identify with PHHP success.

Another type of media, the mini-media, are often underutilized in public-health programming. These include such items as church bulletins and worksite publications. The editors of organizational newsletters/publications are provided with tip sheets, short articles, and other types of materials that assist them with health tips as a regular part of their publication. PHHP also publishes two newsletters of its own, including the BEAT which is designed for mailing to gatekeepers of organizations, volunteers, and other persons interested in our program. A second publication more specifically designed for people at their worksites is "Heart off the Press." Bulletin boards at various organizations constitute another example of useful mini media. Fi-

From the Division of Health Education, Memorial Hospital of Rhode Island, Pawtucket, Rhode Island, the Department of Community Health, Brown University, Providence, Rhode Island, the Department of Medicine, Memorial Hospital of Rhode Island, and the Department of Medicine, Brown University, Providence, Rhode Island.

nally, PHHP has compiled large numbers of names and addresses of individuals throughout the city who either have been found to be at risk on a specific risk factor or have expressed particular interest in receiving materials regarding a given heart-health topic. These registries provide economical and targeted mailing lists for new materials and are used to promote relevant upcoming events.

For large-scale community-wide program delivery, PHHP has developed a number of approaches, many of which can also be applied effectively to large organizations such as churches and worksites. These include campaigns which are designed to spotlight a specific risk factor for a limited period of time, concentrating program resources on this promotion. For example, in respect to cholesterol, the "Know Your Cholesterol" campaign has been especially successful. Another major community-wide approach uses contests. The "Lighten-Up" contest is a weight-loss program held at both worksites and community sites in which people are weighed in during a specific period of time.³ They become eligible to win prizes if they lose a specific amount of weight in a predetermined time frame. An important aspect of this contest is the fact that excessive weight loss, exceeding an average of two pounds per week, makes a person ineligible for the prizes. An average loss of less than one pound per week also renders a participant ineligible. PHHP also sponsors city-wide recipe contests, such as the popular and well-publicized "cookoffs," and a "chili challenge" each summer during which local restaurant chefs compete for the best "heart healthy" chili.

A third type of community-wide approach includes the "Weigh-In." This is a very simple program, conducted on a continuing basis by the City Department of Parks and Recreation, in collaboration with PHHP, during which people are weighed, set specific goals for weight loss, pledge an amount of money or volunteer time toward the achievement of that goal, and return at a later date either to reclaim their money or provide volunteer time if they are not successful.

The physical and social environment powerfully influences how people behave. Accordingly, we have a number of programs designed to make lasting changes in both the physical and social environment of the city to help people be motivated, and change and maintain the new behaviors. These include the Four Heart restaurant program in which low-fat, low-cholesterol, and low-sodium items are marked on the menus of

14 participating restaurants. There are also public cooking demonstrations for low-fat, low-sodium dishes, conducted by chefs from the Four Heart restaurants. In addition to being a popular event with the public, the program also helps motivate the chefs to learn more about low-fat, low-sodium cooking and reinforces both the chefs and their restaurants desire to cooperate. The cooking demonstrations are filmed and form part of our Cable Television programming, thereby also publicizing the restaurants. There is also a worksite cafeteria program in which worksite cafeterias are helped to increase their low-fat, low-cholesterol, low-sodium offerings and to highlight those items which are heart healthy. PHHP staff have also worked with other types of food providers, including helping a local caterer develop a heart-healthy menu for those who wish to have their parties entirely or partially heart healthy. With PHHP help, the local Domino Pizza franchise has designed a delicious pizza, substantially lower in fat and sodium, which has been popular enough to remain on its menus.

Of course another major point-of-purchase environment is the supermarket. A shelf-marking system is in place in all major supermarkets and in a number of the smaller grocery stores in the city of Pawtucket. These include low-fat, low-sodium, low-sodium/low-fat, and high-polyunsaturated-fat indicators. PHHP also provides recipe tear-offs in many of the supermarkets so that new recipes can be obtained at the same time the person is in a position to purchase the ingredients. Some of the healthy eating tip sheets have been used as bag stuffers as well. Supermarkets also provide excellent locations for cholesterol SCOREs and for taste-testing events.

The taste-testing concept is important because many people still have the misconception that low fat, low sodium food is not appetizing. There are many opportunities available to provide such demonstrations. For example, early in the program PHHP staff prepared buffets for the Leadership Committee. More recently staff were able to influence the menu of the Memorial Hospital corporation dinner (which includes many of the leaders of the community), and have assisted in designing menus for Rhode Island Medical Society meetings. In addition to a delicious and healthful menu, handouts were provided for each table emphasizing the fact that it was a heart healthy meal. The extra cost of that useful endeavor was the minimal cost of printing the handouts. A number of churches have also included heart healthy items as part of their church

suppers, labelling the items as such. Finally, PHHP has had nutrition booths at several church fairs and at major community events as well.

PHHP staff also work with a number of special groups throughout the community. Examples of these are the schools in which a heart-health curriculum course is taught by school staff in most of the grades. Recipe contests and heart-healthy cook-offs are conducted by the Home Economics Department. School health fairs are organized by PHHP staff and volunteers. Heart health clubs are taught after school for 4th and 5th graders by health-promotion students from Rhode Island College. These and other heart-health activities are generally carried out by the teachers and staff of the schools in all public and private schools in Pawtucket.

PHHP has also been very active collaborating with physicians because of the pivotal role played by them and the entire medical care system in health promotion. These activities have included mail-outs of new materials on nutrition and cholesterol as they become available, presenting medical conferences at Memorial Hospital, providing frequent program updates at the Pawtucket Medical Association meetings, assisting in the design and delivery of other Continuing Education Courses through Brown University, and referral of large numbers of patients with high blood-cholesterol levels to physicians. PHHP has also attempted to involve physicians' office staff in primary prevention activities. They have been trained to act as group leaders in small group behavior-change programs. Heart-healthy materials are maintained in many physicians' offices so that patients can be encouraged to use them and to use the services of PHHP. Other activities have included assisting the hospital laboratory in remaining up-to-date as new national standards for normal cholesterol levels have appeared, the loan of fingerstick cholesterol assessment equipment to physicians and health clinics, and much cross referral with PHHP with patients referral to physicians for medical care and physicians referring patients to PHHP for such services as nutrition counseling and weight loss assistance. Individuals with high-cholesterol values are tracked and encouraged to take advantage of both educational opportunities and the medical care system. A new effort has been made to actively encourage the screening of cholesterol levels of family members of individuals found to have particularly high cholesterol levels or to have suffered from premature coronary heart disease.

Summary

Health promotion on a community basis can draw effectively on many of the organizations and resources of the community. Use of these resources amplifies efforts to motivate, teach behavior change skills, and maintain heart-healthy practices. The Pawtucket Heart Health Program offers a useful model to other communities planning health promotion programs.

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Before prescribing, please consult complete product information, a summary of which follows:

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides, documented megaloblastic anemia due to folate deficiency, pregnancy at term and during the nursing period, infants less than two months of age.

WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.

BACTRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, pallor, purpura or jaundice, may be early indications of serious reactions. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Perform complete blood counts frequently.

BACTRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Bactrim than with penicillin.

PRECAUTIONS: General: Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (e.g., elderly, chronic alcoholics, patients on anticonvulsants, with malabsorption syndrome, or in malnutrition states) and severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur, frequently dose-related.

Use in the Elderly: May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, e.g., impaired kidney and/or liver function, concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see **WARNINGS** and **ADVERSE REACTIONS**) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly. In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura reported. Make appropriate dosage adjustments for patients with impaired kidney function (see **DOSAGE AND ADMINISTRATION**).

Use in the Treatment of Pneumocystis Carinii Pneumonitis in Patients with Acquired Immunodeficiency Syndrome (AIDS): Because of unique immune dysfunction, AIDS patients may not tolerate or respond to Bactrim in same manner as non-AIDS patients. Incidence of side effects, particularly rash, fever, leukopenia, with Bactrim in AIDS patients treated for *Pneumocystis carinii* pneumonitis reported to be greatly increased compared with incidence normally associated with Bactrim in non-AIDS patients.

Information for Patients: Instruct patients to maintain adequate fluid intake to prevent crystalluria and stone formation.

Laboratory Tests: Perform complete blood counts frequently. If a significant reduction in the count of any formed blood element is noted, discontinue Bactrim. Perform urinalyses with careful microscopic examination and renal function tests during therapy, particularly for patients with impaired renal function.

Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. Keep this in mind when Bactrim is given to patients already on anticoagulant therapy and reassess coagulation time. Bactrim may inhibit the hepatic metabolism of phenytoin. Given at a common clinical dosage, it increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When giving these drugs concurrently, be alert for possible excessive phenytoin effect. Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

Drug/Laboratory Test Interactions: Bactrim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs if methotrexate is measured by a radioimmunoassay (RIA). The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenicity, Impairment of Fertility **Carcinogenesis:** Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim. **Mutagenicity:** Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination; concentrations used exceeded blood levels of these compounds following therapy with Bactrim. Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities. **Impairment of Fertility:** No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

Pregnancy Teratogenic Effects: Pregnancy Category C. Trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefit justifies potential risk to fetus.

Nonteratogenic Effects: See **CONTRAINDICATIONS** section.

Nursing Mothers: See **CONTRAINDICATIONS** section.

Pediatric Use: Not recommended for infants under two months (see **INDICATIONS** and **CONTRAINDICATIONS** sections).

ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION).**

Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia. **Allergic Reactions:** Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. Periorbital nodosa and systemic lupus erythematosus have been reported. **Gastrointestinal:** Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia. **Genitourinary:** Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria. **Neurologic:** Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. **Psychiatric:** Hallucinations, depression, apathy, nervousness. **Endocrine:** Sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, cross-sensitivity may exist. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. **Musculoskeletal:** Arthralgia, myalgia. **Miscellaneous:** Weakness, fatigue, insomnia.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN: Usual adult dosage for urinary tract infections is one DS tablet, two tablets or four teaspoonsfuls (20 ml) b.i.d. for 10 to 14 days. Use identical daily dosage for 5 days for shigellosis. Recommended dosage for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses every 12 hours for 10 days. Use identical daily dosage for 5 days for shigellosis. **Renal Impaired:** Creatinine clearance above 30 ml/min, give usual dosage, 15-30 ml/min, give one-half the usual regimen, below 15 ml/min, use not recommended.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS: Usual adult dosage is one DS tablet, two tablets or four teaspoons (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS: Recommended dosage is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

HOW SUPPLIED: DS (double strength) Tablets (160 mg trimethoprim and 800 mg sulfamethoxazole)—bottles of 100, 250 and 500, Tel-E-Dose® packages of 100. Prescription Paks of 20 Tablets (80 mg trimethoprim and 400 mg sulfamethoxazole)—bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 40. **Pediatric Suspension:** (40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoon)—bottles of 100 ml and 16 oz (1 pint). **Suspension:** (40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoon)—bottles of 16 oz (1 pint).

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in *Rauwolfia Serpentina* (L.) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral α-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
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3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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NECROLOGY — 1987

Edmund A. Sayer, MD

Doctor Edmund A. Sayer, a urologist, died February 5, 1987 at the age of 85.

Doctor Sayer was a graduate of Hahnemann University Medical School in 1925. He interned at the Genessee Hospital, Rochester, NY from 1925 to 1926 and graduated from the School of Aviation Medicine in 1928 as a flight surgeon in the US Army Air Corps. He pursued graduate study at Harvard Graduate School in 1929, the Polyclinic, NY, the Mayo Clinic, Rochester, Minn., the University Hospital at Iowa City, Iowa, Massachusetts General Hospital, Boston, and Cook County Hospital, Chicago.

Doctor Sayer was a junior surgeon at the former Homeopathic Hospital (now Roger Williams General Hospital) and established the department of urology there in 1935 where he was chief of the department until 1974. He served as president of the medical staff at Roger Williams from 1940 to 1942 and on the executive committee for five terms. He was on the hospital board of trustees joint conference committee for two years. He was a consultant in urology for 25 years at South County Hospital and Westerly Hospital and served on the staff of Roger Williams General Hospital for almost 50 years.

Doctor Sayer was a member of the Rhode Island Medical Society, the Providence Medical Association, the Providence Surgical Society, the American Medical Association, the American College of Surgeons, the International College of Surgeons, and the New England Branch of the American Urological Society.

Doctor Sayer was the husband of the late Gertrude L. (Strayer) Sayer.

Augustine W. Eddy, MD

Doctor Augustine W. Eddy, an orthopedic surgeon, died February 14, 1987 at the age of 80.

Doctor Eddy was a graduate of Tufts Medical School in 1932. He served an internship at St Joseph Hospital, Providence, attended the University of Pennsylvania for post graduate studies, and received a fellowship to the Crile Clinic, Cleveland, Ohio. Doctor Eddy maintained a practice in Woonsocket for 40 years before retiring in 1977.

He was chief resident of bone and joint surgical service at Boston City Hospital. Doctor Eddy

started practice in Woonsocket in 1937. He was chairman of orthopedics at Woonsocket Hospital and had served as head of its medical board. He was a fellow of the American College of Surgeons, a member of the American Medical Association, the Woonsocket Medical Society and the staff of Fogarty Memorial Hospital.

Doctor Eddy was the husband of Eleanor (Donlon) Eddy.

Edwin Vieira, MD

Doctor Edwin Vieira, a family practitioner, died February 28, 1987 at the age of 82.

Doctor Vieira was a graduate of Harvard Medical School. While serving in the Navy in World War II and the Korean War, he held the rank of captain and was a flight surgeon. He was school physician for the town of Seekonk and was Medical Examiner for the state of Rhode Island for 12 years; also acting chief in the medical examiner's office for several years. He was a member of the Rhode Island Medical Society and the American Academy of Family Practitioners.

Doctor Vieira was the husband of Mary Elsie (Rosa) Vieira.

John J. Donnelly, MD

Doctor John J. Donnelly, a surgeon, died March 4, 1987 at the age of 79.

Doctor Donnelly graduated from Boston University School of Medicine in 1932. He practiced as a surgeon with offices in Providence for many years before retiring in 1973. Doctor Donnelly was a member of the staffs of both units of St Joseph Hospital since 1943 and was a senior visiting gynecologist at the RI Medical Center since 1946. He was a member of the New England OB-GYN, the Rhode Island Medical Society, the New England Industrial Medical Association and the American Medical Association. He was the surgeon general of the Military Order of Foreign Wars, RI Chapter, National Association. Doctor Donnelly was a captain in the Army Medical Corps in the Pacific Theater during World War II.

He was the husband of G. Madonna (Harlow) Donnelly.

Irving A. Farrell, MD

Doctor Irving A. Farrell, a general practitioner, died March 16, 1987 at the age of 90.

Doctor Farrell graduated from Harvard Medical School in 1924. He maintained an office in Central Falls until retiring in 1970. Doctor Farrell served on the staffs of Memorial, Notre Dame, Roger Williams, and St Joseph Hospitals. He was a member of the Rhode Island Medical Society and American Medical Association.

Doctor Farrell was the husband of Mary E. (Lyon) Farrell.

Joseph C. Johnston, MD

Doctor Joseph C. Johnston, a general practitioner, died March 26, 1987 at the age of 92.

Doctor Johnston was a 1926 graduate of Tufts Medical College. He was on the staffs of the Providence and North Providence units of St Joseph Hospital, the Providence Lying-In Hospital (now Women & Infants), the former Homeopathic Hospital, the former Charles V. Chapin Hospital, and Rhode Island Hospital. He was a former industrial physician for Narragansett Electric Co and Federal Products Co and former police surgeon for the city of Providence. Doctor Johnston was a member of the American and Rhode Island Medical Associations.

Doctor Johnston was the husband of Patricia (Horan) Johnston.

Americo A. Savastano, MD

Doctor Americo A. Savastano, a leading orthopedic surgeon, died April 4, 1987 at the age of 80.

Doctor Savastano graduated from Harvard Medical School in 1932 and trained in New York City. He scored firsts in several treatments never before attempted in Rhode Island, such as reconstruction or replacement of arthritic hips and knees, and the use of surgically implanted steel rods to straighten the spines of scoliosis victims. Doctor Savastano became chief of the Department of Orthopedic Surgery and Fractures at Rhode Island Hospital from 1965 until 1978. He became clinical professor of Orthopedic Surgery at Brown University in July 1973. Earlier he had been an instructor at New York Polyclinic Medical School and Hospital from 1937 to 1945.

Doctor Savastano organized an annual conference on sports medicine at URI, co-sponsored by the Rhode Island Medical Society. He developed the Savastano Vitallium, a total knee replacement and was editor/author of Knee Joint Replacement Surgery, published in 1980. He served as a member of President Johnson's Council on Physical Fitness, and in 1967 was a member of the US team's medical staff at the

Pan-American Games in Winnipeg. Doctor Savastano served a term on the former state Board of Medical Review in the late 1970's. He pushed the General Assembly for legislation to require motorcycle riders to wear helmets and protective clothing.

Doctor Savastano was a fellow of the American Fracture Association, the American Academy of Orthopedic Surgeons, the International College of Surgeons and the American Medical Association. He was a member, often an officer, of many other medical organizations, including Rhode Island Medical Society, Providence Medical Association, New York Medical Society, and the Rhode Island and New England Orthopedic Societies. In 1977 he was inducted into the International Knee Society. In 1959 he received an honorary doctor of science degree of URI, and in 1978, he received an honorary degree from Tokyo Medical College.

Doctor Savastano was the husband of Alda (Winfield) Savastano.

Howard W. Umstead, MD

Doctor Howard W. Umstead, an anesthesiologist, died April 21, 1987 at the age of 74.

Doctor Umstead was a 1938 graduate from Tufts School of Medicine. He was Chief of Anesthesiology at The Memorial Hospital in Pawtucket for 35 years before retiring in 1979.

Doctor Umstead was the husband of Edith (Cumming) Umstead.

John J. Sheehan, MD

Doctor John J. Sheehan, an obstetrician, died April 24, 1987 at the age of 78.

Doctor Sheehan graduated from Tufts University School of Medicine in 1936. He had a practice in Providence from 1938 until retirement in 1982. Doctor Sheehan was on the staff of Women & Infants Hospital and also served on the staffs of Roger Williams Hospital, Memorial Hospital in Pawtucket, St Joseph Hospital in Providence and Our Lady of Fatima Unit, North Providence. He was a member of the Providence and Rhode Island Medical Societies, and the New England Obstetrical and Gynecological Society.

Doctor Sheehan was the husband of Helen (Finley) Sheehan.

Edward A. Ricci, MD

Doctor Edward A. Ricci died August 1, 1987 at the age of 80.

Doctor Ricci graduated from the St Louis Uni-

versity School of Medicine, Missouri in 1934. He was appointed medical examiner for northern Rhode Island in 1939 and served for several years. Doctor Ricci served throughout Europe during World War II with the 5th Surgical Group in evacuation and field hospitals. In 1946 he was appointed physician for the North Providence School Department until retiring in 1985. He was also on the staffs of St Joseph and the former Our Lady of Fatima Hospitals. Doctor Ricci was a member of the American Medical Association, the Providence Medical Association and president of the Malpaghi Medical Society.

Doctor Ricci was the husband of the late Lillian (Vivier) Ricci.

Ralph D. Richardson, MD

Doctor Ralph D. Richardson, a surgeon, died September 24, 1987 at the age of 77.

Doctor Richardson received his medical degree from Harvard University in 1935. After three years as a fellow at the Mayo Clinic in Rochester, Minnesota he earned his masters degree in surgery. An associate professor of surgery at the Brown University Medical School, Doctor Richardson was on the staff of the following hospitals: Rhode Island, Roger Williams General, Women & Infants, Butler, South County Hospitals, and the Veterans Administration Medical Center. He was a member of the New England Surgical Society, the New England Cancer Society, the Providence Medical Association, of which he was past president, the Rhode Island Medical Society, and the American Medical Association. During World War II, he served as chief of surgery with the 136th Station Hospital in the European Theater, where he obtained the rank of colonel.

Doctor Richardson was the husband of Helen (Sinclair) Richardson.

Rocco Bruno, MD

Doctor Rocco Bruno, a general practitioner, died November 12, 1987 at the age of 72.

Doctor Bruno was a graduate of Case Western Reserve Medical School, Cleveland, Ohio. He practiced in the Blackstone Valley from 1945 until his retirement in 1980. Doctor Bruno served as Cumberland school physician for 24 years. He was a company commander in the 6th Army

Medical Battalion during World War II and was awarded two Bronze Stars and the Presidential Unit Citation. Doctor Bruno served on the staff of Pawtucket Memorial Hospital and Notre Dame Hospital in Central Falls. He was a member of the American Medical Association, Pawtucket Medical Association, and Rhode Island Medical Society.

Doctor Bruno was the husband of Margaret (Lanigan) Bruno, RN.

Richard L. Testa, MD

Doctor Richard L. Testa, a surgeon, died November 15, 1987 at the age of 51.

Doctor Testa was a graduate of University of Bologna Medical School in Italy. He served as an Army surgeon with the 945th Surgical KA Team, 93rd Evacuation Hospital, Long Binh, Tay Ninh, and Chu Lai, Vietnam, in 1966 and 1967. Doctor Testa practiced general surgery from 1969 to 1985 at St Joseph Hospital, Providence, and Roger Williams General Hospital. He was a past president of the St Joseph Hospital medical staff.

At the time of his death, he was medical director of Blue Cross/Blue Shield and medical director at Providence College. Doctor Testa was a member of the American Medical Association, the Rhode Island Medical Society, the Providence Medical Association, and one of its past presidents, the Providence Surgical Society, and the American Burns Association. He was a certified member of the American Board of General Surgery, and a fellow of the American College of Surgeons.

Doctor Testa was the husband of Elaine A. (Magliano) Testa.

Frederick J. Fay, MD

Doctor Frederick J. Fay, a surgeon, died November 19, 1987 at the age of 67.

Doctor Fay was a 1953 graduate of Jefferson Medical College in Philadelphia. He began a private practice in Providence in 1958 after being chief resident in surgery at Mercy Hospital, Pittsburgh, PA from 1956 to 1958. He later moved his office to Cranston in 1980, retiring in 1984.

Doctor Fay was a member of the Rhode Island Medical Society, the American Medical Association and the American College of Surgeons.

Doctor Fay was the husband of Helen M. (Doherty) Fay.

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HAVE YOU HEARD?

Clinical trials for THA are to be launched at 17 trial site locations according to Dr. T. Franklin Williams, Director of the National Institute on Aging (NIA). The THA clinical trials represent the Alzheimer's Disease and Related Disorders Association's (ADRDA) first joint effort with the NIA and the Warner-Lambert Company, a worldwide healthcare products company leading the area of cognitive and memory research. The five million dollar study, designed to be completed in two years, will test THA with approximately 300 Alzheimer patients at sites throughout the country to measure the safety and effectiveness of the drug. The results of a preliminary study citing improvement in 16 or 17 AD patients treated with THA which appeared in a *New England Journal of Medicine* (November 13 1986) report prompted the launching of extensive clinical trials. Researchers feel that by increasing the amount of acetylcholine in the brain, the presence of THA may relieve some memory impairment in AD patients.

• • •

\$90 million could be saved each year if all two-year-old US children are vaccinated against *Haemophilus influenzae* type b (Hib) disease. This from a study published in the September issue of *Pediatrics* showing a cost of two billion annually in health care and social costs due to Hib disease. *Haemophilus influenzae* type b is the most common cause of bacterial meningitis in children, regarded as the leading cause of acquired mental retardation in the United States. Most victims are under five years of age and between five-ten per cent die. Children who survive meningitis (25 to 33 per cent) have long-term complications such as retardation, seizures, and hearing problems. Vaccination recommended for children at the age of 24 months, and provision of preventive antibiotic medicine to exposed contacts are two preventive strategies for Hib infection explored in the article. Benefits from disease prevention would include reduced medical treatment and diagnostic costs and decreased levels of social support services for children with permanent handicaps due to Hib infection. Joel Hay, PhD, of the Hoover Institution at Stanford University and Robert Daum, MD, of the Department of Pediatrics at Tulane University Medical School, conducted the study.

Progress in fighting liver disease during the past year has included release of a genetically engineered vaccine against hepatitis B, and a dramatic growth in liver transplants, with more than 1,500 expected in 1987. Also, more effective screening of blood is becoming possible through research to isolate the non-A, non-B viruses transmitted through blood transfusions. According to Thelma King Thiel, president of the American Liver Foundation, the present available vaccine should prevent the hepatitis B cases that occur annually in the United States. Development of a more effective test for the non-A, non-B hepatitis viruses would prevent hepatitis cases resulting from blood transfusions.

• • •

Through tests of sulfasalazine, an antibiotic used in the treatment of ulcerative colitis, people with ankylosing spondylitis, or spinal arthritis, may have new hope. From reports in a recent *Arthritis Today*, tests show that the drug may actually treat the disease itself, instead of just treating symptoms. Painful symptoms of the spine are relieved without the usual adverse side effects common with other medications used to treat ankylosing spondylitis. Stiffening of the spine and other problems resulting from spinal arthritis could be slowed down or prevented through use of sulfasalazine.

Seeking referrals for Multiple Clinical Studies

Clinical Programs Ltd. is now testing new psychiatric drugs for patients with depressive illness or anxiety disorders. If your patient is showing symptoms of either, he/she may do well in one of these carefully monitored studies. FREE evaluation, lab testing and treatment if selected. Appropriate referral, if not. All results can be made available to referring physician. For further information or consult, call Walter Brown, M.D. or June Petrucci, RN, 274-4949, 272-1022.

PERIPATETICS

At the third International Conference on AIDS held in Washington, DC, **Dr Kenneth H. Mayer**, chief of infectious disease at Memorial Hospital of Rhode Island, was associated with five presentations. **Dr Mayer** presented a lecture for an interdisciplinary course about the AIDS epidemic at the Harvard School of Public Health. Dr Mayer addressed the New England regional conference of the State Health Department HIV Counselors at the Massachusetts State Laboratory Institute recently and presented a paper in a symposium on "Modes of HIV Transmission" at the National Meeting of the Society for Epidemiological Research in Amherst, Mass.

• • •

Dr Larry Culpepper, research director of Family Medicine at Memorial Hospital of Rhode Island, was appointed as one of three members on an ad hoc committee of the board of the Society of Teachers of Family Medicine. The committee will work with other family medicine organizations over the next four to six years to improve the research funding climate for family medicine.

• • •

The American Rheumatism Association's annual meeting in Washington, DC was attended by **Dr Faiza Fawaz Estrup**, chief of rheumatology at Memorial Hospital of Rhode Island. **Dr Estrup** participated in a panel discussion on arthritis at Brown University.

• • •

Honored recently for their dedicated service to the hospital and the community were three Woonsocket Hospital physicians. **Dr Ernest L. Dupre**, an obstetrician, has been a member of the medical staff since 1954. Joining the medical staff in 1951, **Dr Wilfred V. Ethier** served first as an anesthesiologist, and later as a general practitioner. **Dr George M. Kokolski**, internal medicine, has been a member of the medical staff since 1969. They are retiring after a combined total of 86 years of service to The Woonsocket Hospital.

Dr Richard A. Carleton, Physician-in-Chief and Chief of Cardiology at Memorial Hospital of Rhode Island, has recently been appointed a member of the National Disease Prevention, Education and Disease Control Advisory Committee for the National Heart, Lung and Blood Institute. **Dr Carleton** has also been appointed as a convener for the Society of Preventive Cardiology which meets annually in conjunction with the American Heart Association.

• • •

The journal, "Psychosomatics," recently appointed **Dr Richard J. Goldberg**, associate professor of psychiatry and human behavior and psychiatrist-in-chief at the Rhode Island Hospital, as an assistant editor. He will be responsible for a special section of the journal called "Primary Care and Psychiatry."

• • •

On invitation to be a visiting professor in Jakarta, Indonesia, **Dr Carroll M. Silver**, clinical professor of orthopaedics emeritus, spent three weeks there in October 1987. **Dr Silver** taught the indications and surgical techniques in cerebral palsy and post-polio deformities which are common in Indonesia.

• • •

A nephrologist and Clinical Assistant Professor of Medicine at Brown University, **Dr Marc S. Weinberg** was recently made a Fellow of the American College of Physicians. He was also awarded the Banice Feinberg Physician of the Year Award for 1987 on behalf of the American Heart Association, RI Affiliate.

• • •

Dr Mary D. Lekas, chief of Ear, Nose and Throat Service at Rhode Island Hospital, recently attended the Society of University Otolaryngologists as part of the 98th Annual Meeting of the Association of American Medical Colleges in Washington, D.C. While in Washington, she was a Visiting Professor at the Walter Reed Medical Center.

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Caution patients about the combined effects of Limbitrol with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car. In general, limit dosage to the lowest effective amount in elderly patients.

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References: 1. Feighner JP, et al. *Psychopharmacology* 61: 217-225, Mar 22, 1979. 2. Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

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Tranquilizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use; then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone—drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring



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reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extra-pyramidal symptoms, syncope, changes in EEG patterns

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritis

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. IV administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly. Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

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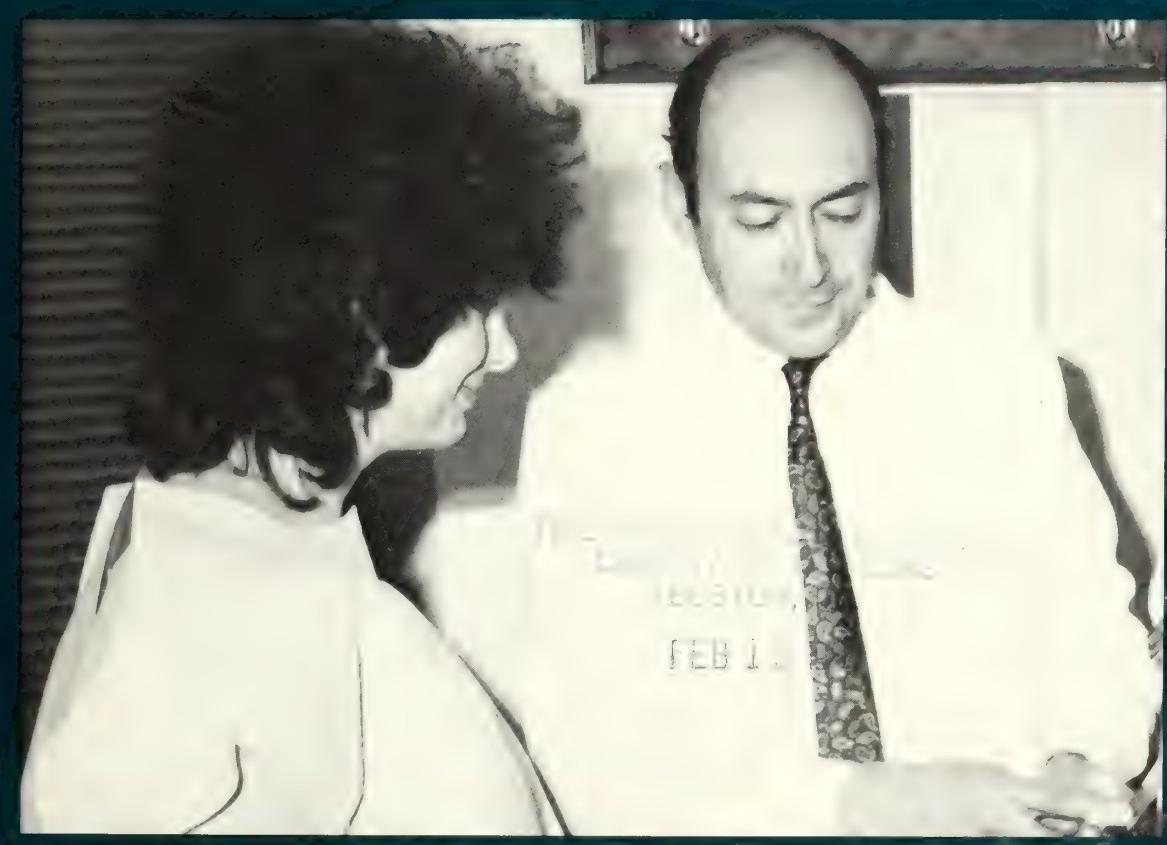
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THE BENEFITS OF CANCER SCREENING

(see page 55)

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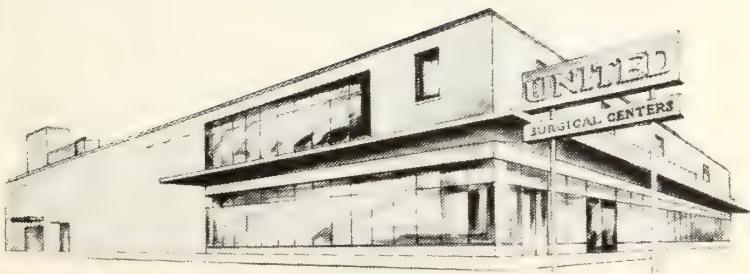
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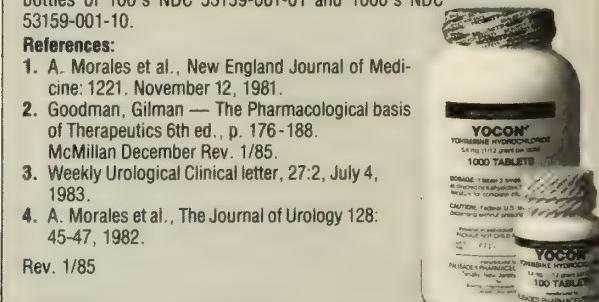
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

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References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
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EDITORIAL

A Full Plate

The number, scope, and dollar value of medical projects for which state certificate-of-need (CON) authorization is currently being sought is unprecedented. There are no less than thirteen proposals already made or in prospect totaling \$14.5 million. Others are in the planning phase. Rhode Island Hospital (RIH) alone has plans for a regional children's hospital (replacing the 46-year-old Potter Building), new and expanded adult intensive care units (to replace the once pioneering, but now outmoded and inadequate facilities in the Main Building), a new cardiac catheterization unit, and eventual floor-by-floor renovation of the Main Building opened in 1955. The pediatric hospital, to be built adjacent to the new Women & Infants Hospital, will contain 95 beds and will be connected to the Main Building by walkways. The Davol Building at RIH, opened in 1983, was designed to accommodate additional floors above the current emergency and operating rooms. The CON application will include a request for five additional floors to house updated and expanded cardiac catheterization facilities, modern intensive care units, and shell space to provide for additional beds to replace those eventually lost in the renovation of the Main Building, which now has many outmoded and crowded 4-bed nursing units. Rhode Island Hospital will also be involved with Cranston General Hospital in a 20-bed rehabilitation unit in addition to its own 8-bed unit, and hopes to be associated with Kent County Memorial Hospital in a cardiac catheterization unit. Six hospitals are currently seeking such units, while the Health Services Council is likely to approve only three.

Another large project that will be presented soon is the transfer of Bradley Hospital, a respected and pioneering children's psychiatric hospital in East Providence, to the RIH campus. This, coupled with the new children's hospital and the highly regarded neo-natal capabilities of Women & Infants Hospital, will provide a state-of-the-art full-service regional children's medical center for Rhode Island and nearby Massachusetts.

Another large proposal is the merging of Fogarty Hospital in North Smithfield near the Woonsocket line with Woonsocket Hospital, which would involve several new services, including cardiac catheterization and a drug and alcohol abuse unit. Roger Williams General Hospital currently has under construction a new emergency and ambulatory facility, and envisions the establishment of a cancer center in the old Lying-In Hospital building, which it acquired after Women & Infants Hospital moved to the RIH complex.

These projects are "frightening" to some members of the Rhode Island Business Group and to the Health Services Council, which must approve them. The RIH projects alone amount to \$96.5 million. There is likely to be some drastic winnowing because of capital spending limits imposed by CONCAP, a compact comprising the Hospital Association of Rhode Island, the state budget office, and Blue Cross and Blue Shield of Rhode Island. CONCAP, determined by negotiation, is the increase in operating costs of the state's health-care system deemed affordable. It measures the estimated increased interest and

depreciation costs associated with the capital spending. CONCAP in 1987 was \$2.5 million dollars, covering \$25 million in capital expenditures. If everything submitted for 1988 were approved, the CONCAP would have to be \$11.4 million, unlikely to be found acceptable.

It is difficult to make a sound judgment in a situation like this, where, with the possible exception of a few cardiac catheterization laboratories, everything appears to be so desirable and forward-looking. With the Brown University medical school rapidly gaining prestige, it is highly desirable that RIH become a medical center of world-class capabilities. Finding the money to build and to maintain it is a major problem for this small state of fewer than a million souls. There is little development involved here, however, which is purely visionary. As Rhode Island's economy is changing progressively from its manufacturing base to one of service industries, it is important that its medical care and medical education institutions be equal to those anywhere. We now have a well-functioning medical school which Usher Parsons and William Osler, each in his day, argued that we in Rhode Island should provide and could afford. Osler at the turn of the century said: "The money should be the least difficult thing to get in this plutocratic town" —

perhaps an overstatement in these times of fiscal restraint, but still not without validity. Development of first-class affiliated institutions is not an irrelevant issue.

The Health Services Council must somehow perhaps, with prudence, but certainly with foresight, find a way to make most of these ambitious and desirable projects a reality.

Seebert J. Goldowsky, MD

New RIMJ Cover Design

As each year often brings change and fresh beginnings, so the JOURNAL has also seen a slight alteration. With the January 1988 issue we introduced a new cover design. The familiar cover had been part of the JOURNAL format since 1980. By removing the table of contents from the cover, the photograph and caption are now the main focus. This, along with a different logotype, creates a simpler, concise look. We hope that the result is both attractive and functional to our readers.

Kimberly J. Allyn

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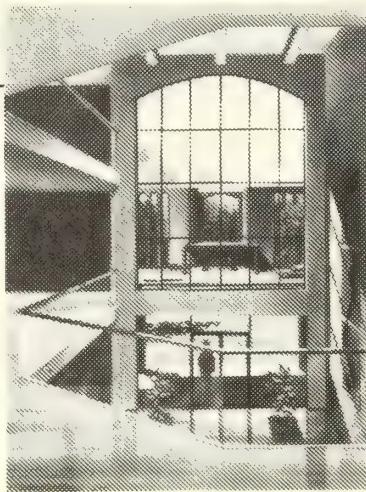
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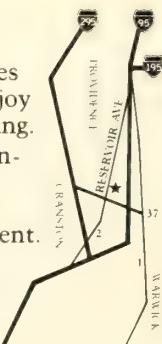
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Cancer Control in Rhode Island: Part II. The Roger Williams Cancer Screening Program

This Preliminary Study Has Demonstrated the Value of the Process

Julie G. Beitz, MD
Alan B. Weitberg, MD

By all criteria the level of usage of cancer-screening procedures in the United States leaves much room for improvement. While numerous reasons can be cited, first and foremost is the imperfect nature of the information base. The American Cancer Society (ACS) guidelines for the cancer-related check-up¹ were devised to assist physicians and patients alike in making important decisions in early cancer detection. They are based on evidence from controlled and uncontrolled studies, as well as on clinical judgment. As new information becomes available from continuing clinical trials, these guidelines will have to be reassessed periodically. For the present, however, the current guidelines offer an excellent starting point.

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From the Division of Hematology/Oncology, Roger Williams Cancer Center and the Department of Medicine, Brown University, Providence, Rhode Island. Part I of the series appeared in the October 1987 issue of this Journal.

In response to the growing concern over the rising cancer mortality rate in Rhode Island, a comprehensive cancer-screening program, based on ACS guidelines, was established at the Roger Williams Cancer Center in October 1985. The goals of this program were: 1) to inform the public about the lifesaving potential of early breast, cervical, and colorectal cancer detection, and 2) to facilitate access to annual screening examinations and bring those in need of additional care into the mainstream of the health care system. This report will summarize the results of cancer-screening activities during the first fifteen months of the program.

Methodology

Participants in the program are recruited through advertisement of the program on local television, radio and newspapers. Initially, participants complete a self-administered written questionnaire which assesses knowledge of cancer-risk factors and current health practices related to cancer prevention and early detection. Next, a medical oncologist records a cancer-oriented history and performs a physical examination, while demonstrating breast or testicular self-examination techniques. Finally, a small group session is conducted by an oncology nurse specialist who reviews self-examination techniques using anatomical models and summarizes risk factors and methods of cancer prevention. The entire program takes 60-90 minutes to complete at a charge of \$50.

Individuals are scheduled for additional screening or diagnostic tests as recommended by ACS guidelines or as dictated by the individual's history or physical findings. Individuals with clinically suspicious findings, eg, of the skin, oral cavity, breasts, or pelvic organs, are referred for follow-up care to their private physicians or when appropriate to subspecialists. Laboratory studies are summarized in writing and mailed to the participants and to their private physicians if they so desire. Participants are invited by mail to return to the screening center annually.

Results

Demographic Characteristics of the Participants. During the first fifteen months of the program, 436 individuals (280 women, 156 men) participated. Fully 95 per cent were Rhode Islanders, while the remainder came from Massachusetts, Connecticut, and New Jersey. Table 1 summarizes some of the demographic variables that characterized these individuals. The majority were female, and two-thirds were 50 years old or older. The frequency of cigarette smoking in this group was below the national average, especially for males. A majority reported a history of cancer in first and second degree relatives. Often, the death of a family member from cancer prompted the visit to the screening center. While 9 per cent at presentation gave personal histories of cancer, one-half of them were basal-cell skin cancers. No persons were undergoing treatment for malignant disease or had evidence of recurrent disease at the time of the screening visit.

Cancer Risk Factors: Knowledge and Practice. Responses to questionnaire items related to cancer-risk factors highlighted some of the strengths and weaknesses of the public's knowledge in this area. The vast majority of respondents were aware

that cigarette smoking (76 per cent), excessive sun exposure (81 per cent) and a family history of cancer (83 per cent) increased one's risk of developing cancer. With regard to dietary factors, such as low-fiber and high-fat intake, only 53 and 63 per cent of respondents respectively, were aware of the association of these factors with increased cancer risk.

Seventy-one per cent of participants believed that cancer could be prevented, while 80 per cent thought that cancer prevention should begin early, ie, before age 40. When asked about current cancer-preventive practices, 61 per cent stated they avoided cigarettes, 72 per cent avoided excessive sun exposure, 52 per cent changed their dietary intake, and 53 per cent had annual cancer-related check-ups.

Frequency of Cancer Detection Tests in Participants Prior to Screening Visit. Participants were asked to report the frequency with which selected screening examinations had been performed prior to their visit to a cancer screening center. These examinations included breast self-examination, breast physical examination, mammography, digital rectal examination, fecal occult blood testing, and Papanicolaou (Pap) smears. The proportions of men and women having such tests were summarized in the first part of this series. To reiterate, the most utilized screening test was the Pap smear: 85 per cent of women under 40 had had a Pap smear within three years of their visit to the screening program. Although levels of testing for other cancer sites were not particularly high, figures for breast cancer detection measures (self-examination, physical examination, mammography) were comparable to national figures.² The proportions of individuals, aged 50-70, having digital rectal examinations and fecal occult blood tests within the last three years were somewhat lower than the national average.³ The discrepancy in the usage of detection measures for colorectal cancer may be explained by the fact that colorectal cancer screening is a much more recent practice than screening either for cervical or breast cancer.

Breast Cancer. Histories taken from the 280 women participants revealed the majority to have no symptoms related to breast disease, either benign or malignant. Ten per cent gave histories of fibrocystic disease and less than 5 per cent reported new symptoms such as breast tenderness or new breast mass. Breast physical examination revealed normal findings in 238 (86 per cent), fibrocystic changes in 29 (10 per cent), and suspicious masses in 15 (6 per cent). These find-

Table 1. Characteristics of Participants (N = 436)

	N	%
Men	156	36
Women	280	64
Age < 50	144	33
Age ≥ 50	292	67
Residence in Rhode Island	414	95
Family History of Cancer	321	74
Personal History of Cancer	38	9
Current Smokers		
Men (N = 156)	25	16
Women (N = 280)	69	25
Former Smokers		
Men (N = 156)	76	49
Women (N = 280)	80	34

ings are summarized in Table 2.

Mammograms were recommended to: 1) asymptomatic women with normal breast examinations who were 50 years old or more, or who were 35-40 and had not had a baseline study, and 2) symptomatic women with or without abnormal examinations over 35 who had not had a mammogram within the last three months that could be reviewed at the screening center.

A total of 134 women had received mammograms, representing a compliance rate of 79 per cent with screening recommendations. Nearly all studies were performed by the radiology department of the Roger Williams General Hospital, although in selected cases studies were performed at facilities nearer to the woman's residence. Of these studies, 17 revealed a suspicious mass with or without calcifications. Eleven studies were in asymptomatic women with normal physical examinations.

All of eight breast biopsies recommended on the basis of physical examination, mammographic findings or both were completed. The ratio of benign to malignant findings was 7.0 to 1, comparable to a ratio of 5.4 to 1 in the Breast Cancer Detection Demonstration Project.⁴ One woman who was discovered to have had a Stage I breast cancer underwent conservative surgery and postoperative radiotherapy and is currently without evidence of disease after 6 months.

Cervical Cancer. A total of 147 women underwent pelvic examinations and Pap smear tests. Pap results were reported as Class I (normal smear, no abnormal cells) in the majority of cases and as Class II (atypical cells) in only 5 instances. Gynecologic referrals were made in 13 cases to evaluate additional problems which were identified, such as abnormal vaginal discharge or uterine enlargement.

Table 2. Screening for Breast Cancer

Source of Finding	Number (%)
<i>Symptom History</i>	N = 280
Asymptomatic	240 (86)
Fibrocystic Disease	29 (10)
New Breast Mass	7 (3)
Breast Tenderness	4 (1)
<i>Exam Findings</i>	N = 280
Normal	238 (86)
Suspicious Breast Mass	15 (6)
Fibrocystic Changes	29 (10)
<i>Mammogram Findings</i>	N = 134
Normal	108 (80)
Mass ± Calcifications	17 (13)
Fibrocystic Changes	9 (7)

Table 3. Screening for Colorectal Cancer

Source of Finding	Men No. (%)	Women No. (%)
<i>Symptom History</i>	N = 156	N = 280
Asymptomatic	120 (77)	236 (84)
Rectal Bleeding	12 (8)	14 (5)
Colonic/Rectal Polyps	10 (6)	3 (1)
<i>Exam Findings</i>	N = 144	N = 227
Normal	128 (89)	203 (89)
Suspicious Rectal Mass	3 (2)	6 (3)
<i>Fecal Occult Blood Test</i>	N = 143	N = 219
Negative	142 (99)	207 (95)
Positive	1 (1)	12 (5)
<i>Fecal Occult Blood Test, Mailed</i>	N = 78	N = 129
Negative	69 (88)	119 (92)
Positive	7 (12)	10 (8)
<i>Sigmoidoscopy</i>	N = 53	N = 91
Normal	37 (70)	54 (59)
Rectal Polyps	5 (9)	7 (8)
Benign Pathology	11 (21)	30 (33)

Colorectal Cancer. Careful histories revealed a number of irregularities related to the gastrointestinal tract. For example, 26 persons with a history of rectal bleeding and 13 with a history of colorectal polyps were identified. Clinically suspicious findings included a palpable rectal mass in 2 per cent (9/371) and positive fecal occult blood tests in 4 per cent (13/362). Persons aged 40 and over were sent home with two additional fecal occult blood test cards (six slides) and instructed in their use and dietary restrictions. Approximately one-half of these individuals returned cards in the mail, enabling the identification of an additional 14 individuals with positive tests (14/207 or 7 per cent). These findings are displayed in Table 3.

Flexible sigmoidoscopies were recommended to all asymptomatic men and women aged 50 and over who had not been studied in the last three years. In addition, persons with positive fecal occult blood tests or palpable rectal masses were recommended to have sigmoidoscopy at the very least, or colonoscopy or both. The majority of studies were performed by a gastroenterologist and a general surgeon on the staff of the Roger Williams General Hospital. Compliance rates with sigmoidoscopy recommendations were fairly high: 68 per cent for men and 73 per cent for women. Of a total of 144 completed studies, 12 revealed rectal polyps. Sigmoidoscopy and colonoscopy together identified a total of 15 individuals with colorectal polyps, 12 hyperplastic and three adenomatous. Studies on the 27 individuals found to have positive fecal occult blood tests thus far have revealed adenomas in two cases and

carcinoma in another. The latter was a Duke's Class A lesion that was completely resected.

Skin Cancer. Careful examination of the skin identified 24 individuals with suspicious lesions referred to a dermatologist for biopsy. A variety of premalignant and malignant lesions have been identified, including congenital giant nevus, melanoma *in situ*, and basal-cell skin carcinoma.

Discussion

This report summarizes the findings to date on the first 436 individuals who participated in the Roger Williams Cancer Screening Program between October 1985 and January 1987. The strength of this program lies in its interdisciplinary approach and the integration of hospital services into a comprehensive cancer detection program. ACS guidelines were readily incorporated into a hospital-based clinical practice and resulted in a dramatic increase in the usage of several cancer detection measures. For example, in the case of mammography, the percentage of women aged 50 to 70 screened by this method approached the projected National Cancer Institute (NCI) objective of 80 per cent for the year 2000.³

As we enter the second year of the program, we hope to complete evaluations of abnormal physical findings, assess the effectiveness of public education by determining whether efforts to reduce risk factors and improve health-care practices had been initiated, and improve compliance further, in particular with respect to the returned fecal occult blood tests, through closer follow-up by phone, mail, or both.

The cost of finding a cancer early in an asymptomatic individual can be readily justified if the cancer is discovered in a curable stage, even if the disease is relatively rare (as most cancers are). However, increased survival is only one measure of the effectiveness of a cancer screening program. Other benefits such as improvement in quality of life and reduction of pain are more difficult to quantify. Similarly, the discomfort of a sigmoidoscopy or the morbidity of a workup for a false-positive test can be difficult to assess. The best screening program would be one that offers a balance of benefits and risks. We believe that the implementation of ACS guidelines into a hospital-based screening program enables a careful and consistent evaluation of patients, so that the problems of overdiagnosis and unnecessary discomfort can be overcome.

Conclusions

As the cancer death rate climbs, screening activities in Rhode Island and elsewhere must be increased. To succeed in reducing the mortality from cancer, efforts must be intensified in three broad fields: public policy, education, and research. These activities can be summarized as follows: 1) establish a steering committee to coordinate cancer screening activities statewide; 2) establish screening programs for cancer at several sites, eg, at hospitals or community health centers, with attention to quality control; 3) encourage third-party payers to reimburse for screening tests and examinations; 4) improve public awareness of the value of screening through education programs in the schools, in the workplace, at senior citizens' centers, and other arenas; 5) include cancer screening in the curricula of medical schools, in residency training programs, and in post-graduate medical courses; and 6) support research on cancer screening technology and on utilization of screening techniques.

Acknowledgments

The authors are indebted to the physicians and nurses of the Roger Williams Cancer Center for their support of the Cancer Screening Program.

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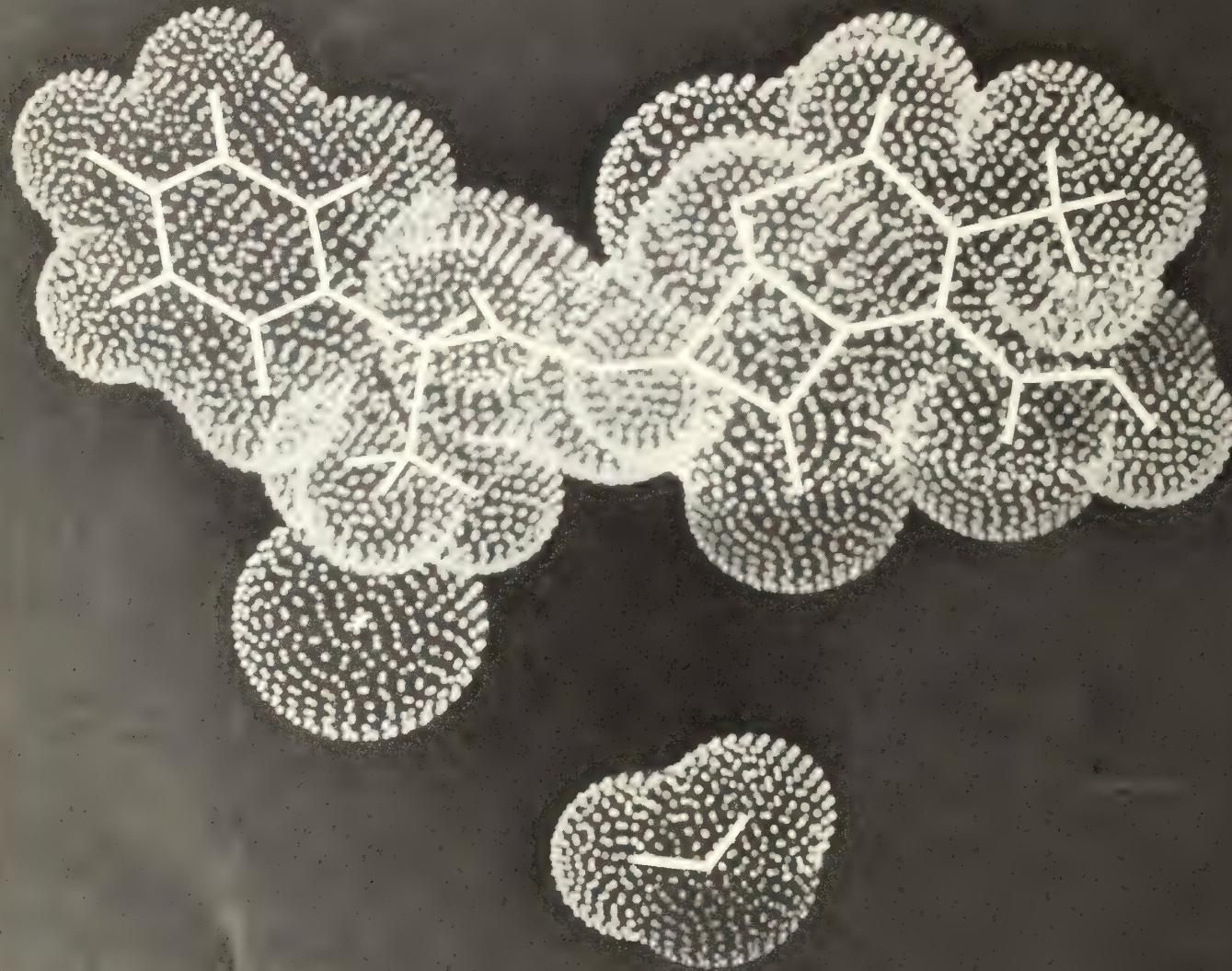
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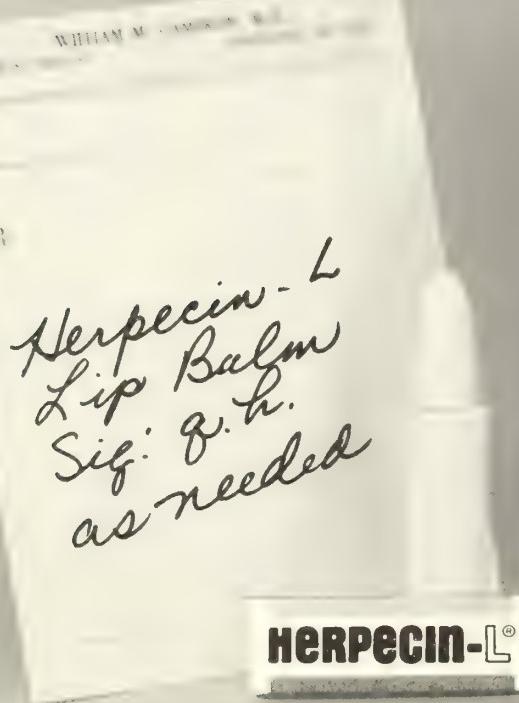
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Richard A. Carleton, MD
R. Craig Lefebvre, PhD

As more and more evidence became available in the late 60s and early 70s from studies such as Framingham,¹ that cardiovascular disease (CVD) was related to behaviors such as diet, smoking, and physical activity levels, the first major large-scale attempts to reduce the overall risk of cardiovascular disease in large populations were attempted.²⁻³ These early studies were followed by three large-scale community research and demonstration studies funded by the National Heart, Lung and Blood Institute. One, based at Stanford University,⁴ began in 1977 and was a direct

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outgrowth of the earlier Three Community Study. The second, based at the University of Minnesota,⁵ was followed six months later by the beginning of the Pawtucket Heart Health Program (PHHP), as described in a paper in this series.⁶ While all of these studies have taken a somewhat different approach, a common theme has emerged: each has sought to effect behavior change in an entire population. The behaviors that are known to increase the risk of cardiovascular disease can be changed. These behavior patterns, however, are entrenched in society, so that the educational and other support efforts required to effect them on a large scale require many resources. Much of the early work in the modification of these behavior patterns was based on individual therapy sessions or small groups led by highly trained (and expensive) professionals. It became obvious that it was simply impractical and not economically feasible to provide intensive one-to-one professional-to-client help for each citizen of an entire community. Thus, the population strategy has been adopted as a vehicle to stimulate significant reductions in CVD morbidity and mortality.

It is well established that many of the behavior choices augmenting risk of coronary disease such as nutritional and dietary habits, smoking, and physical inactivity are learned behaviors. Many aspects of our social and physical environment are important in the initiation and maintenance of these negative health factors. In order to achieve a lasting change in their behavior patterns, it was concluded that these environmental influences had to be modified and, if possible, turned into healthful, positive influences. Thus, in 1979 a small group of researchers at Memorial

Hospital/Brown University submitted a proposal to the National Heart, Lung and Blood Institute to test a community activation approach to health promotion, an approach that would rely heavily on indigenous resources, and be cost-effective. The strategy planned was to build into the fabric of the community itself the educational and support structures needed to change the overall environment to reduce those behavior habits associated with increased risk of cardiovascular disease and ultimately to reduce the rates of morbid and mortal cardiovascular events. In the past five years of intervention activity, we have learned a great deal both about how to mobilize existing resources in support of this effort and about how to market prevention efforts to gatekeepers of community resources for health promotion programs likely to be sustained for the foreseeable future.

The term resources refers to such things as money, personnel, time, communication channels, educational and skill building materials and programs, and elements in both the social and physical environments that will facilitate and maintain pro-healthful behavior patterns. The balance of this paper will include brief descriptions of effective community resources that PHHP has utilized and that are likely to exist in virtually any community in the country.

Since a comprehensive primary prevention program requires the accomplishment of many diverse tasks, a major resource has to be the personnel committed to the project who carry it out on a day-to-day basis. One major source of such personnel are volunteers. We have found them to be abundant, with over 2,000 having served with PHHP in its first five years. We have also found that even in very complex roles they can be cost-effective.⁷ Volunteers are also members of the social networks, groups, and organizations targeted for change and as such already have access and credibility. It is important to note that they are also targets of the intervention themselves and that the very act of learning to help others is a powerful change process in itself. Vol-

unteers not only change their own behavior, but others see that change, and understand the implications this has for their own ability to change. The diffusion of specific behavior-change skills and information is greatly facilitated. Even though volunteers may "officially" be working for the project only a few hours a week, they are continually discussing what they have learned with their friends, relatives, and anyone else who will listen.

This is the fifth and final paper of a series describing the structure and goals of The Pawtucket Heart Health Program. The first two papers appeared in the December 1987 issue and the third and fourth papers appeared in the January 1988 issue of this Journal.

While volunteers can be found in the community at large, they are often most efficiently recruited through organizations. It is also through the various organizations in a community that most of the other types of resources required for primary prevention activities can be most effectively mobilized, or acquired, or both. Among the largest such organizations are religious organizations.⁸ We have found churches to be very receptive to the inclusion of primary prevention education as part of their overall mission. The concepts of spiritual and physical health are very compatible. Religious organizations generally reinforce volunteerism and service to the community as an esteemed activity for its members. They have the facilities that are so critical to programming. Further, churches are located in virtually every neighborhood throughout a community. In addition to people and physical facilities, they also have excellent channels of communication including church bulletins, bulletin boards, church programs and pulpit announcements for promotion, and in some cases actual behavior change information. They also have major events throughout the year that lend themselves very readily to health education (eg, church suppers, bazaars).

Another important source of volunteers and programming are the health related agencies such as the American Heart Association, the American Cancer Society and the American Lung Association. Many of these organizations are already conducting relevant programming. Rather than duplicating their services, our resources are used to promote and refer clients to their existing programs. In turn, we have been able to help

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these agencies find facilities for their groups because of our extensive contacts with religious organizations, social organizations, and the business community.

Social organizations such as the Lions Club, the Rotary Club, and the Portuguese Social Club have community services as one of their major goals. Thus they can provide access for personnel to their organizations, funds, public relations expertise, and enthusiasm. They search for relevant and rewarding types of activities to help their community. These organizations have expert, committed, and respected members. For example, at Octoberfest each year the Rotary Club provides a large number of members and spouses who help with risk-factor screening, counseling, and referring activities.

Community government with its large number of different activities, responsibilities, and departments has proven to be particularly responsive to PHHP. One of the most successful liaisons has been with the Department of Parks & Recreation. In 1982 the Department of Parks & Recreation decided to introduce programming to take advantage of the large numbers of facilities already available. The initial emphasis was on exercise. We approached the leadership, who agreed that, if we would train leaders, they would introduce smoking-cessation, weight-loss, and nutrition classes as part of their schedule. We also trained additional aerobic dance instructors and helped to promote enrollment for each semester. From the time we began, the enrollment in Exercity has risen from approximately 300 per semester in a two-semester system to close to 1,000 per trimester in a trimester system. This collaboration was strengthened by a cooperative agreement in which our exercise physiologist joined the staff of the Department of Parks & Recreation with each of us paying half of his/her salary. They have students that can be taught about CVD by existing teachers or as part of the schools' regular mission. (A Heart Health curriculum course is now in all public and private schools in Pawtucket.) Other resources we have found available have been facilities, home economic classes, health classes, and the school nurses. The schools are also worksites with a large number of employees.

An important community resource often overlooked by health promotion advocates is the local library. We have used the library facilities for classes and as sites for cooking demonstrations. The library staff have also been helpful in distributing information on upcoming events and

in furnishing space for heart-health displays and for recruitment of volunteers. The resource librarians in most libraries are continually seeking the most appropriate books and other educational materials for the library. By suggesting carefully screened materials, organizations such as PHHP can help reduce the number of unsound, fad-nutrition, and other types of self-help health books and video tapes in the library and encourage the acquisition of the best materials available.

Educational institutions such as colleges and universities are often very interested in joint programming, as it provides a forum for student placement in actual community health-education activities. For example, local health-education students from Rhode Island College are the teachers for our Heart Health Clubs and smoking-prevention programs in the schools. The faculty are also often interested in research projects, analyses of existing data sets, and development and testing of new programs or program elements. In addition to faculty and to student placements, campuses are also good locations from which to solicit all types of volunteers. Students are often sensitive to the need to increase their professional experience and begin developing their resumé for post-graduation employment. Finally, colleges provide an excellent source of paid personnel at very low prices through work-study programs. Non-profit agencies such as hospitals qualify for placement of students, generally for 15 hours per week, with the non-profit agencies being responsible for only 30-35 per cent of the base salary. Technical schools also provide an excellent source both for work-study students and for students desiring work experience. For example, the local technical school has courses in phlebotomy. Their students gain much experience by drawing blood for cholesterol assessments. Their nursing students learn to measure blood pressures and become involved in providing some basic nutritional counseling in the field. We also provide an excellent environment for students to practice their microcomputer and word processing skills in a real-life work environment.

A major expense of any kind of community-wide programming involves promotion and other uses of the mass media. While we will occasionally purchase an advertisement in the local newspaper, we received much more help in ways that do not cost us money. For example, the local newspaper provides a bi-weekly column in which we can present new information concerning car-

diovascular disease prevention, teach behavior-change skills, and highlight and reinforce individuals and organizations that are making significant contributions to the overall effort. Local newspapers are also very receptive to ideas for feature stories. Such articles may involve success and human-interest stories, reports on events such as cooking demonstrations or heart-healthful recipe contests, and other publicity that both teaches and promotes the concepts of risk-factor reduction. These can be submitted in several ways. Volunteers or staff members sometimes write feature stories and submit them to the newspaper. We have also found that simply presenting a number of ideas to the local newspaper editor often results in the newspaper itself sending a reporter to cover a story. We are providing the newspaper with a very valuable source of ideas for stories which, after all, is what sells their newspapers. We have also had published series that have been written by student interns. For example, three years ago, a medical student with the ambition of being a medical writer wrote for the local newspaper an excellent series of articles on cholesterol. Finally, we have let the editorial staff know that we are available for questions when any new national development is announced (eg, a new cholesterol drug, results from relevant studies). This not only assures that accurate information is available to the community, but also continues to build program credibility throughout the community.

While we have avoided using commercial television and radio for teaching because of experimental design reasons, we are making more and more extensive use of cable television with its free access and free use of equipment and facilities. It is less expensive and more efficient to obtain a relevant film and have it shown on cable television with appropriate publicity than it would be to obtain the same film and simply show it at the local library. More people will tune in their television sets than will leave their homes for any specific program. Also, these same films can be shown on several different occasions without additional cost. Local radio and television have been extensively involved with promotion of upcoming events, and others could use them as partners in teaching as well. Like newspapers, they accept feature stories, need experts for analyses, and run public service announcements. The cable companies are often very short of any type of public access programming and thus very willing to cooperate. In addition to films produced by others, we have produced an exercise show and

have also filmed some of our cooking demonstrations conducted by local chefs for rebroadcast on cable television. This gives reinforcement to the chef, the restaurant, and our program with filming of the demonstration being the only cost. When done by staff, or volunteers, or both, with the cable television equipment, this can be done at minimal cost.

Still another important type of partners are the local businesses and industries. The Blackstone Valley Chamber of Commerce has established a Heart Health Committee which helps in determining needs and in promoting health-promotion programming. Through them we have assisted local businesses and industries in establishing smoking-constraint policies, in adapting cafeterias to provide heart-healthier selections, and in helping provide SCOREs as well as behavior-change groups and other types of programmings at local worksites. Over 50 local worksites have active programming. We have also found individual businesses willing to donate contest prizes, services, and money to maintain and expand our programming. We have found our local restaurants and supermarkets to be willing to donate such things as \$10-\$50 grocery shopping certificates, food for events, and coupons for discounts on meals.

An obvious source of support and resources for primary prevention activities are the local medical groups and organizations. For example, Memorial Hospital of Rhode Island as a worksite has been particularly supportive both in allowing programming to take place with its employees and in taking a leadership role in adopting and disseminating new information in the fields of primary prevention through grand rounds, newsletters, and sponsorship of outside speakers. The Public Relations Department provides a source of expertise for promotion of various activities. Family Medicine residents have enthusiastically adopted the fast turnaround finger-stick devices for measuring total cholesterol levels and do basic nutrition counseling to help their patients lower high cholesterol levels.

The physicians in the hospital and throughout the community have been a major source of support and expert advice. From service on a very early Physician Advisory Committee to the local medical society sponsorship of our most recent smoking-cessation contest, including purchasing of banners and t-shirts and allowing the organization's name to be used in promotion, our physician community has been extraordinarily supportive. Individual physicians have accepted

and effectively worked with large numbers of citizens whom we have identified as having either high blood-pressure or high-cholesterol levels. In return, many of the physicians have referred their patients to PHHP for weight-loss, cholesterol-reduction through diet, smoking-cessation, and establishment of effective physical-activity programs. Many of the physicians maintain copies of our various self-help materials in their offices so that patients can more easily order them from PHHP. Finally, several of the physicians have had office staff trained to help patients to conduct weight-loss and smoking-cessation programs for their patients.

The Rhode Island Department of Health is an invaluable source of materials and expertise. We utilize a number of the different booklets that they have developed and have called upon their professional staff from time to time to act as unpaid advisors. They have jointly sponsored several of our major evaluation activities, helping to provide the necessary credibility to assure high survey-response rates.

Any community-wide program has large amounts of material that must be assembled, booklets to be put together and stapled, and envelopes to be stuffed. We have found our local housing projects for the elderly and handicapped to be excellent sources of this type of help. For example, we have cooperated with one such project (Towers East) for a number of years, with each Thursday being materials assembly day. After new materials are printed or acquired, such as those that go into self-help kits, we take them to Towers East, where they are introduced into an assembly line which, with appropriate quality control, provides a very labor-intensive part of any programming to be done at no cost to us. These committed citizens, as do so many others in the program, gain a real sense of fulfillment and involvement.

Summary

Virtually any group or organization in the community has a potential for involvement in primary prevention activities. Examples presented are but a few of the innovative ways to activate a community for health.

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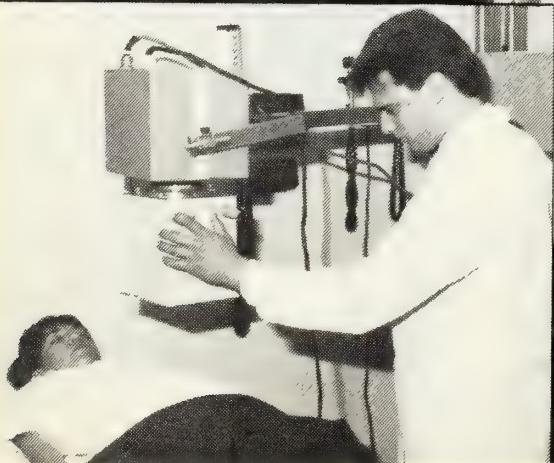
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Medical Practice Variation in the Management of Acute Medical Events in Nursing Homes: A Pilot Study

Better Structuring of Physician Nursing Home Practice Will Facilitate More In-House Management of Acute Episodes

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Medical care in nursing homes (NH) is often inadequate. It is characterized by discontinuity, over

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reliance on hospital emergency room, and unnecessary hospitalizations.^{1, 2}

Potential barriers to effective medical care include physician preoccupation with office and hospital patients and the lack of reliable, trusted liaison between the doctor and his/her nursing home patients by a nurse practitioner.³ Medicare and Medicaid reimbursement policies are also barriers. Reimbursement regulations such as the number of patients who may be seen per day in a given home or the allowable number of visits per month for a given patient are designed to thwart the unscrupulous overutilizer. Regrettably, at the same time such rules impede physicians motivated to give good care. There are also psychological impediments which result from the sense of hopelessness which commonly surrounds these profoundly incapacitated patients.

In our review of the literature we found several studies which examined patient transfers to emergency rooms and hospitals. We found none which looked first at acute medical events and their subsequent disposition, that is, management in the nursing home, hospital emergency room (ER) transfer and return to NH, or ER transfer and hospital admission. We decided that it would be useful to carry out such a study in several NHs and compare the results.

Methods

Four licensed nursing homes with reputations for competence and concern were approached about participating in the study. All volunteered. The characteristics of the homes are described in Table 1. Two were for-profit, while two not-for-profit. Bed capacity ranged from 108 to 254. All homes had skilled nursing and intermediate care facility (ICF) I beds, while three also had small numbers of ICF II rest-home beds. All operated at near maximum census. The study period covered an interval of four months from June to September 1985. We retained a nurse researcher, who managed all interviews, data collection, and data tabulation.

Defining an acute medical event turned out to be a perplexing problem. Initially we sought some taxonomy-embracing signs, symptoms, and diagnostic categories. This task became hopelessly complex. We finally defined an acute event from the perspective of the nursing director or the

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charge nurse. Any episode which required non-routine unplanned physician consultation was included in the study. We did not review elective surgical or medical hospitalizations. To ascertain a working measure of how many events might be encountered per month, we asked each nursing director to review retrospectively all records for acute events which took place in the month of June. Commencing in July all acute events were recorded as they occurred. This activity continued for three months. The nurse researcher recorded the nature of the event, the patient's characteristics such as age, diagnoses, length of stay, activities of daily living (ADL) score, the type of physician involvement such as phone contact or visit to the home, and the management decisions made. Sources of data included the NH record, interviews with nursing staff, interagency referral forms, ER and hospital discharge reports. The nurse researcher also prepared a summary of each acute event by NH in order to understand the relative severity of the acute events and to judge whether there were major disparities in the case mixes of the four NHs.

Two types of measures were produced to describe the experience of each nursing home in respect to the incidence and treatment of acute problems among its patients. One measure was a rate based on the average daily census for each home. Such rates were computed for the number of acute medical events (AMEs), transfers to emergency rooms, and inpatient admissions. The second measure was a percentage based on the number of AMEs occurring in each institution. Such percentages were computed for transfers to emergency rooms and inpatient admissions. For each measure, the result for each nursing home was compared with the combined figure for the other three facilities. Statistical significance was determined by testing for the difference between two population proportions using the two-tailed test with the normal distribution. Significant differences at the level of .10, .05, and .01 are reported in the section on results.

Results

We identified 102 acute medical events during the study period, ranging from eighteen to twenty-nine per home. The rate of acute events (per 100 average daily census) varied from 11.6 in nursing home B to 22.8 in nursing home C. The values for both nursing homes at the extremes were found to be significantly different ($p < 0.01$) when each was compared to the three other nursing homes combined (Table 2). Review

Table 1. Characteristics of Sample Facilities, 1984

Auspice	A		B		C		D	
	For-Profit		Non-Profit		For Profit		Non-Profit	
Total Beds	168		254		129		108	
	#	%	#	%	#	%	#	%
SNF	68	40	100	39	52	50	24	22
ICF I	98	58	119	47	69	53	84	78
ICF II	2	1	35	14	8	6	0	0
Average Daily Census	165		251		123		107	
Average Age of Patients	83.5		85.4		81.5		82	
Hospital In-Pt Adm/100 ADC*	59		65		65		11	
Number MDs Visiting	39		38		19		15	

* Based on a full year of experience

Table 2. Acute Medical Events: Hospital Transfer and Admission Rates

Rates for Four Month Period	Nursing Home			
	A	B	C	D
Rate of Acute Event per Average Daily Census	16.4 (NS)	11.6 (p<0.01)	22.8 (p<0.01)	16.8 (NS)
Rate of ER Transfer per Average Daily Census	7.9 (NS)	7.6 (NS)	13.0 (p<0.01)	1.9 (p<0.01)
Rate of Hospital Admission per Average Daily Census*	6.1 (NS)	6.0 (NS)	7.3 (NS)	2.8 (p<0.10)

* Including both direct admissions and admissions through the hospital ER.

Table 3. Characteristics of Acute Medical Events Patients

	Nursing Home				Total
	A	B	C	D	
Total Number	27	29	28	18	102
Percent Skilled	30%	14%	18%	22%	21%
Average Age	84	85	82	82	83
Percent Female	59%	79%	57%	100%	72%
ALS First Admission*	16 mos.	50 mos.	28 mos.	21 mos.	29 mos.
ALS Last Admission†	9 mos.	16 mos.	17 mos.	19 mos.	20 mos.
Functional Status§					
A — 0, 1, 2	0%	10%	11%	0%	6%
B — 3, 4	26%	21%	25%	17%	22%
C — 5, 6	74%	66%	57%	78%	68%
D — Unknown	0%	3%	7%	5%	4%
Functional Status 3, 4, 5, 6	100%	87%	82%	95%	90%

* Average length of stay since first admission at this nursing home including intermittent time spent in other care settings.

† Average length of stay since the most recent admission at this nursing home.

§ 1 = highest or best functional status, 6 = lowest or worst functional status.

of the case summaries revealed no major differences in severity of acute events among the four NHs. The general characteristics of patients experiencing acute medical events are displayed in Table 3. The functional status of these patients appears to be very similar. Furthermore, the differences in rates of acute events could not be explained by structural factors, ie, differing distributions of skilled nursing and intermediate care

beds in the four nursing homes. Although 37 per cent of the beds in the four nursing homes were classified as skilled nursing beds, only 21 per cent of acute medical episodes occurred among patients in skilled beds. In nursing homes taken individually, the overwhelming majority of acute medical episodes occurred among intermediate care patients. Thus, differences in bed distribution could not explain differences in the

Table 4. Signs and Symptoms Associated With Acute Medical Events

	#	%
1) BP and pulse change	35	17.5
2.) Behavioral change	24	12.0
3) Respiratory distress	21	10.5
4) Temperature change	21	10.5
5) Joint pain/limited ROM	17	8.5
6) Neuro changes	15	7.5
7) Falls	13	6.5
8) GI distress	12	6.0
9) Abnormal lab/EKG	10	5.0
10) Chest pain	9	4.5
11) Appetite change	7	3.5
12) Circulatory change	5	2.5
13) Abdominal pain	5	2.5
14) Foley cath/G-tube problems	5	2.5
15) Urinary output change	1	0.5
Total	200	100

patterns of care and hospital use among the nursing homes examined.

Signs and symptoms associated with the acute medical episodes were classified into fifteen categories (Table 4). Half fell into the following four groups: 1. blood pressure and pulse change, 2. behavioral change, 3. respiratory distress, and 4. temperature elevation. Each event was associated with 1.9 signs and symptoms. Six diagnostic categories accounted for 72.5 per cent of the acute episodes: cardiovascular 27.3 per cent, infections 14.7 per cent, fractures/joint problems 11.7 per cent, gastrointestinal (GI) bleeding 7.8 per cent, psychiatric disturbance 5.8 per cent, and seizures 4.9 per cent.

Fifty per cent of acute episodes occurred within six months of the most recent admission to the NH. Seventy-six per cent had severely impaired ADL scores of five or six. We had no patient controls for these variables.

The patients attending physicians managed fifty per cent of acute episodes. A covering physician responded to 28 per cent, while a medical resident or nurse practitioner responded to 14 per cent. The NH medical director managed the remainder (Figure 1). Fifty-seven per cent of acute events in NH C were responded to by covering physicians. In NH B medical residents handled 25 per cent of acute events while in NH D a nurse practitioner managed 38 per cent. Physicians responded most often except for NH C, where group coverage was provided. Medical residents played an important role in NH B, while nurse practitioners played a key role in NH D.

Fifty-three per cent of the physicians responded within an hour of notification. Seventy-

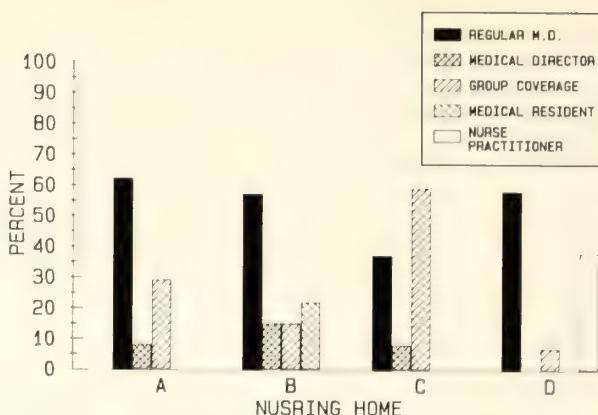


FIGURE 1. PHYSICIAN INVOLVEMENT WITH ACUTE MEDICAL EVENTS IN NURSING HOMES

five per cent responded by telephone alone, four per cent by phone and visit to the NH, and seventeen per cent by a visit to the home. Physicians already in the NHs at the time the events occurred accounted for seventeen of eighteen visits (Table 5).

Forty-nine per cent of the patients experiencing acute episodes were transported to a hospital ER: Institution A = 48 per cent, B = 66 per cent, C = 57 per cent, and D = 11 per cent. When each institution was compared to the other three participants as a group, the rates for B and D were found to be significantly different than those for their peer institutions. Of patients transferred to the hospital ER, 74 per cent were admitted: Institution A = 77 per cent, B = 74 per cent, C = 56 per cent, and D = 100 per cent. Thirty-five per cent of all of the patients experiencing acute episodes were admitted to a hospital, either through the ER or directly: Institution A = 37 per cent, B = 52 per cent, C = 32 per cent, and D = 17 per cent. Again the percentages for B and D were found to be significantly different than those for the other participating nursing homes (Table 6).

It is of particular interest that NH D had a

Table 5. Acute Medical Events Physician Response Mode

Nursing Home	Phone	Visit	Phone and Visit	No Response	Total
A	23	1	2	1	27
B	17	10	1	1	29
C	24	2	1	1	28
D	13	5	0	0	18
Total	77	18*	4	3	102
%	75.4%	17.6%	3.9%	2.9%	100%

* In 17 of the 18 cases, the physician was already in the facility at the time of the event.

Table 6. Percent Emergency Room Transfer and Hospital Admission for Acute Medical Events in Four Nursing Homes*

	Nursing Home			
	A	B	C	D
Acute Medical Events (AME)	27	29	28	18
Percent AMEs Transferred to Emergency Room (Significance)	48.1	65.5	57.1	11.1 (NS) (p<0.05) (NS) (p<0.001)
Percent of AMEs Transferred to ER, Admitted to Hospital	77	74	56	100
Percent AMEs Admitted to Hospital† (Significance)	37.0	51.7	32.1	16.7 (NS) (p<0.05) (NS) (p<0.10)

* For four months.

† Total admitted including direct admissions from the nursing home and admissions through the hospital ER.

small percentage of patients transferred to the ER or hospital, and of the few transferred all were admitted. In contrast NH C had nearly half of its ER transfers returned to the home. NHs A and B both had a high proportion of their ER transfers subsequently admitted to the hospital.

For each nursing home the *rate* of transfers to the ER and the *rate* of hospital admissions (per 100 average daily census) was compared to average rates for the other three nursing homes combined. Nursing homes A and B were found to have rates that were not significantly different from average, whereas C and D were significantly different in their rates of hospital transfer ($p<0.01$). Nursing home C had the highest rate of transfer of all four homes at 13.0, while NH D the lowest at 1.9. Nursing home D exhibited a marginally significant difference ($p<0.10$) from its peer institutions in rate of hospital admissions — at 2.8 per 100 average daily census. Rates of hospital admission for the other three homes were grouped in the range 6.0-7.3 (Table 2).

Discussion

This study reveals that physicians and NHs may vary substantially in their practice patterns in the presence of acute medical episodes. Our data suggest that the physicians at NH D managed many acute events "in-house," while those at the other NHs did not. Additionally, when they transferred a patient to the hospital, the patient in every instance was judged appropriate for admission. Analysis of the characteristics (func-

tional status, age and percentage in skilled nursing beds) of the AME patients demonstrates a strong comparability among the patients in each of the NHs.

Why then is there such a striking variation in nursing home and physician practice? We suspect that several factors play a role. The first factor involves the structure of the physician's practice in relation to his NH patients. For instance, if the relationship between the nursing home and the physician is long-standing, communication and trust between unit nurses and physicians is facilitated. The fewer physicians that a NH must deal with, the better the communication. The use of an "in-house" nurse practitioner with physicians available as backup by telephone has already been demonstrated to improve care and reduce ER referrals and hospitalization of NH patients.³

The practice pattern of physicians at NH D is as follows. For many years NH D has had a closed medical staff of approximately fifteen physicians. Patients who are candidates for admission or their families, or both, are apprised in advance of the arrangements for medical care. Each staff physician takes a two- to four-month rotation during which time he/she is responsible for patients on one or two floors. For the most part the doctors have worked in the home for many years and have come to know the nurses, who themselves have a long tenure of service. About eight years ago NH D hired a nurse practitioner who spends much of her time on the floor with the most acute patients, but who is available to all the patients. She has gained the respect of the physicians, who have developed considerable confidence in her judgment. This trust permits many complex issues to be reviewed and decisions made via telephone consultation. Most who work in this setting are convinced that this relationship greatly reduces the number of patients who might otherwise end up in an ER for evaluation. It also results in the NH being able to manage quite ill patients such as those who experience exacerbations of congestive heart failure or who contract pneumonia or urosepsis or suffer other serious problems. Success in this team approach to managing such problems builds confidence among the staff, and also enhances morale and pride in work. Our observations reinforce the recommendations of several studies which advocate wider use of nurse practitioners in NHs.⁴⁻⁷

On contrast, the relationship of physicians to the three other facilities is on a more individu-

alistic basis (ie, non-group or team). On the average, there are 32 physicians having an interface with the nurses in NHs A, B, and C. Turnover of physicians in these homes is based on relationships with individual patients. In Rhode Island, the number of patients a given physician may happen to have in a given institution ranges from one (57 per cent of the visiting MDs) to 60 (8 per cent of the visiting MDs).⁸ Clearly, at either extreme communication about an AME in a given patient may be impaired. At the time of this study, only one of the four facilities employed nurse practitioners.

A second factor accounting for the variation in performance among nursing homes may be the distance from the NH to a hospital. This was not considered explicitly as a factor which could influence the decision to transfer a patient. Obviously, a long trip of thirty to sixty minutes might influence a physician or nurse to order an ambulance rather than observe a patient. In this regard NHs A, B, and D are all within three miles of a hospital. In contrast NH C is eighteen miles from the nearest hospital. This may explain in part the higher transfer and return rates observed for NH C.

Given the pilot nature of our study, its brief duration, and the relatively small number of acute events evaluated, our conclusions must be considered to be preliminary. More comprehensive investigations should be carried out. In particular, we recommend efforts to deal more critically with the issue of comparable case mix. While our case-by-case review revealed no differences among the NHs in the severity of cases, it is conceivable that we overlooked data which might have offered an alternative explanation for our observations.

Furthermore, this study did not initially collect statistics regarding multiple admissions of individual patients. It would be desirable in future studies to compare NHs with respect to the percentage of admissions which were re-admissions for the same or different problems. This would improve our evaluation of a NH's relative ability to manage acute events and keep patients' problems stabilized.

It is frequently observed that the transfer of frail elderly persons to hospitals is a jarring disruptive experience, which is often associated with new disorders or worsening of established problems. Thus, it is important that we devise mechanisms and programs which permit nursing homes to manage more acute illness. We have observed that this can be accomplished if the

practice of physicians in nursing homes is properly structured.

We suspect that patients will benefit clinically from having acute problems managed in the nursing home, and also that federal programs will be spared considerable expense. Demonstrating this will not be simple and poses another challenge for future studies.

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To report an ADR by phone, call **456-ADRS** weekdays between 9 and 5. To receive mailing forms and additional information, call the Health Department at 277-2901.

HAVE YOU HEARD?

A recent *Arthritis Today* article reports that oral gold, a treatment for rheumatoid arthritis, can be used safely and effectively in children with the disease. From a collaborative study by a group of pediatric rheumatology research centers across the United States, results show that children visiting their doctors for an injection of gold may now take their gold medication by mouth, without the inconvenience or pain of injection. This is the first study showing that the drug can be used safely in children.



A study by the National Cancer Institute (NCI) shows that many young adults today who survived cancer as youths can look forward to having children. NCI scientists assessed the risks to fertility posed by various cancer treatments in 2,283 survivors of childhood and adolescent cancer in the largest study of its kind. The study, examining effects on fertility of cancer treatments given 12 or more years ago, concluded that treatment for childhood and adolescent cancer that was given before 1975 reduces female fertility by only up to 7%, but reduces male fertility by up to 24%.



Panic disorder may be caused by a gene on chromosome 16, according to a recent study in *Archives of General Psychiatry*. 26 families with a history of panic disorder were studied by R. R. Crowe, MD, of the University of Iowa College of Medicine, Iowa City, and colleagues, by looking at various genetic markers in an effort to determine where the disorder may be genetically linked. The strongest association was found between panic disorder and the presence of one marker known to be on chromosome 16, a red blood cell antigen called alpha-haptoglobin. The authors say that, although this association was not quite statistically significant, their analysis provides "suggestive evidence" that a gene for panic disorder may be located near the marker.



Along with documentation of neurologic problems in adults with AIDS, similar reports have surfaced involving children with AIDS and AIDS-related complex (ARC). Central nervous system dysfunction in a large series of young patients with symptoms of human immunodeficiency virus (HIV) infection has been noted from a report in January's *American Journal of Diseases of Children*.

dren, AJDC. These problems were found in 61 of 68 HIV-infected infants and children studied by Anita Lesgold Belman, MD, of the State University of New York Health Science Center at Stony Brook, NY, and colleagues. Complications included acquired microcephaly (abnormally small head size), cognitive impairment, and other deficits. Authors say the clinical courses of most of the children varied from static to steady deterioration; only a handful showed improvement over time.



Laser flow cytometry, discovering the presence of malignant cells and other cells that cause disease much sooner, is having a tremendous impact on the treatment of human disease. A computer-driven instrument, the laser flow cytometer examines a cell's volume and complexity by laser and allows physicians to actually evaluate a patient's immune system. Clark Springgate, MD, an immunopathologist at the Oschner Medical Institutions in New Orleans, says, "For diagnosis and prognosis, it's a very significant advance," adding that its ability to predict the probable course and outcome of disease, as well as to detect cells that look benign but are really malignant is probably most important.

PERIPATETICS

Dr Horace F. Martin, director of Clinical Chemistry at Rhode Island Hospital, will serve as a consultant to the Clinical Toxicology Devices Panel for the US Food and Drug Administration. **Dr Martin** will work to insure that safe and reliable results are obtained from instrumentation used in the clinical laboratory.



Recently, in Amsterdam, the Netherlands, **Dr Ivor M. D. Jackson**, director of the Division of Endocrinology at Rhode Island Hospital, spoke on the role of the drug Somatostatin Analogue in the treatment of Acromegaly, a form of pituitary tumor. **Dr Jackson** was one of four investigators invited from the United States.



The Memorial Hospital in Pawtucket has announced recent appointments to its medical staff: **Dr Gary K. Lundstrom** in radiology; **Dr Donya A. Powers** in family medicine; **Dr Daniel S. Harrop, III** in psychiatry; and **Dr David C. Yoburn** in nephrology.

Before prescribing, see complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: While a weak antiandrogenic effect has been demonstrated in animals, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity in humans.

In a 24-month toxicity study in rats at dose levels approximately 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'.

Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of 'Tagamet' HCl [brand of cimetidine hydrochloride] injection by intravenous bolus.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states have been reported on occasion, predominantly in severely ill patients.

'Tagamet' has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg. q.i.d. or 800 mg. h.s. concomitantly with a 300 mg. b.i.d. dosage of theophylline [Theo-Dur®], Key Pharmaceuticals, Inc.,

demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg. h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. [Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.]

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken in patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: Diarrhea, dizziness, somnolence, headache, rash. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Gynecomastia and reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses, for at least 12 months, have been reported. Reversible alopecia has been reported very rarely. Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and a few cases of aplastic anemia have also been reported. Increased serum transaminase and creatinine, as well as rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including hypersensitivity vasculitis, have been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly un-

likely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported.

How Supplied: Tablets: 200 mg. tablets in bottles of 100; 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 [intended for institutional use only]; 400 mg. tablets in bottles of 60 and Single Unit Packages of 100 [intended for institutional use only], and 800 mg. Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 [intended for institutional use only].

Liquid: 300 mg./5 ml., in 8 fl. oz. (237 ml.) amber glass bottles and in single-dose units (300 mg./5 ml.), in packages of 10 [intended for institutional use only].

Injection:

Vials: 300 mg./2 ml. in single-dose vials, in packages of 10 and 30, and in 8 ml. multiple-dose vials, in packages of 10 and 25.

Prefilled Syringes: 300 mg./2 ml. in single-dose pre-filled disposable syringes.

Plastic Containers: 300 mg. in 50 ml. of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.

ADD-Vantage® Vials: 300 mg./2 ml. in single-dose ADD-Vantage® Vials, in packages of 25.

Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored at controlled room temperature. Brief exposure up to 40°C does not adversely affect the premixed product.

'Tagamet' HCl (brand of cimetidine hydrochloride) Injection premixed in single-dose plastic containers is manufactured for SK&F Lab Co. by Travenol Laboratories, Inc., Deerfield, IL 60015.

* ADD-Vantage® is a trademark of Abbott Laboratories.

BR-TG-L73B

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without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium. Use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids), and during concurrent use with amphotericin B or corticosteroids or corticotropin (ACTH). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency.

Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions.

Blood dyscrasias have been reported in patients receiving triamterene and leukopenia, thrombocytopenia, agranulocytosis and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide. Dose adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine.

Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indometacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The

following may occur: transient elevated BUN or creatinine or urine hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, slurred speech, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

BRS-DZ-L45

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The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or

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Caution patients about the combined effects of Limbitrol with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car. In general, limit dosage to the lowest effective amount in elderly patients.

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References: 1. Feighner JP, et al. *Psychopharmacology* 61: 217-225, Mar 22, 1979. 2. Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

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Tranquillizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady state concentrations of the tricyclic drugs. Concomitant use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring

reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extra-pyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, olopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. IV administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestations and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly. Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: Double strength (DS) Tablets, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and Tablets, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt). Available in bottles of 100 and 500. Tel-E-Dose® packages of 100. Prescription Paks of 50.



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12.5 mg amitriptyline (as the hydrochloride salt) ^{IV}

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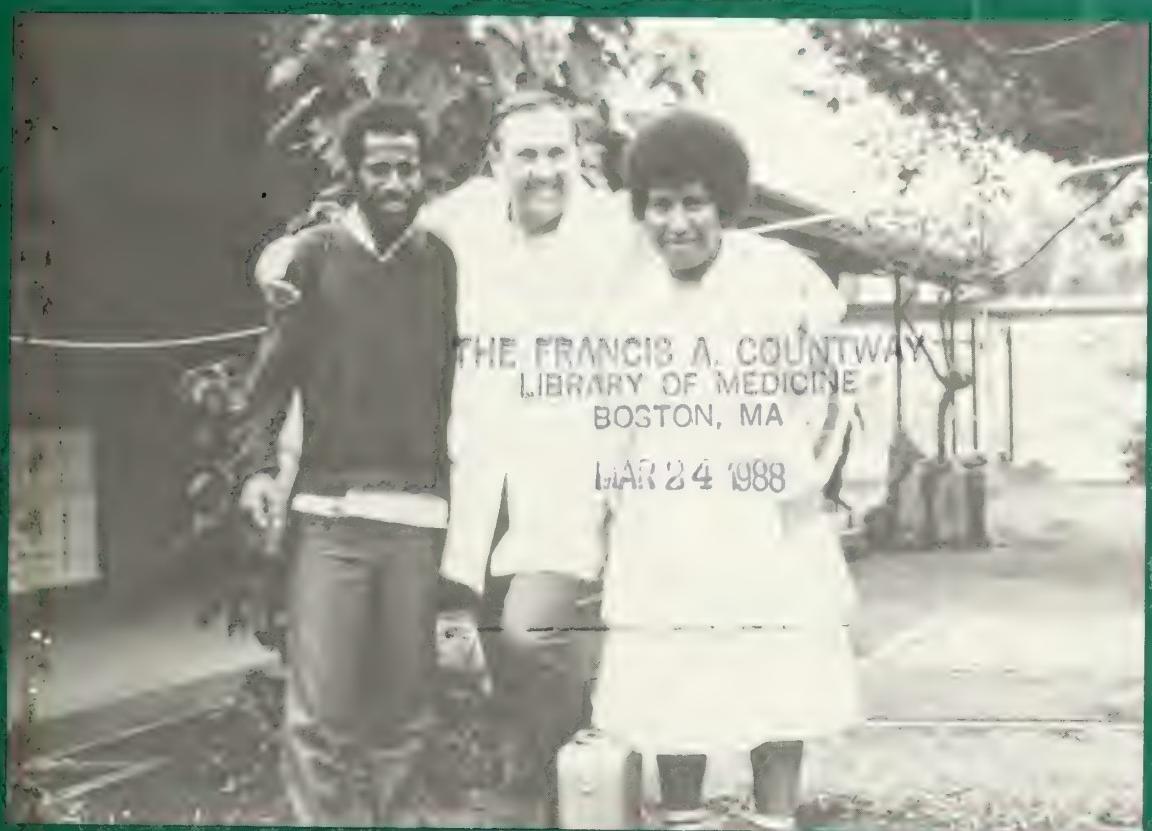
Please see summary of product information on adjacent page.

RHODE ISLAND MEDICAL JOURNAL



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Volume 71, Number 3



A SURGEON'S LIFE IN PAPUA NEW GUINEA

(see page 99)

WHO IS BEST QUALIFIED, AND WHO CAN BEST BE TRUSTED TO KNOWLEDGEABLY PROTECT THE RHODE ISLAND PHYSICIAN

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ISA HILLEL ATWOOD JOY BURT BOOTH ARVIN DONG VERNNA JACQUELINE
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ADFOR DORA BROOKE PAYNE SYLVIA JULIANA Y CALLOWELL JOSEPH
ORRIS EL VIRA EL ROY WARTON NOEL DEREK BUDO JUDD CRAVEN
VALKER BRAD MERVIN SYDNEY LEONORA JANE A HENRIETTA BRAD
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AUL GUNTHER FELIX RALPH NATHANIEL SEAN WALLACE BEATRICE SIEYL CARA MILDRED ARNOLD GREGORY HUMPHREY
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ON

...like the more than one million patients who have received INDERAL® LA.

In a recent survey, 4,120 participating physicians gave us their views¹ on INDERAL LA in the treatment of hypertension, angina and migraine.

INDERAL LA is their preferred beta blocker

...of the nearly three out of four physicians responding to the questionnaire, an impressive 97% rated INDERAL LA good to excellent for overall performance. Virtually all cited efficacy, tolerability, long-term cardiovascular protection and once-daily convenience as important factors in their choosing to prescribe INDERAL LA.

INDERAL LA promotes patient compliance

...Virtually every responding physician rated patient satisfaction with INDERAL LA to be as good as, or better than, other beta blockers.

Like conventional INDERAL Tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree and bronchial asthma.

ONCE-DAILY
INDERAL LA
(PROPRANOLOL HCI)
LONG ACTING
CAPSULES
60, 80, 120, 160 mg

The one you know best keeps looking better

Please see next page for brief summary of prescribing information.

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ONCE-DAILY
INDERAL LA
(PROPRANOLOL HCl)

LONG ACTING CAPSULES
60, 80, 120, 160 mg

The one you know best keeps looking better

60 mg 80 mg 120 mg 160 mg

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL[®] LA brand of propranolol hydrochloride (Long Acting Capsules)

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. Inderal is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by Inderal, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Inderal LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with Inderal LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of Inderal Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

Inderal LA should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to Inderal LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, Inderal LA has been therapeutically equivalent to the same mg dose of conventional Inderal as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. Inderal LA can provide effective beta blockade for a 24-hour period.

INDICATIONS AND USAGE. Hypertension: Inderal LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. Inderal LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: Inderal LA is indicated for the long-term management of patients with angina pectoris.

Migraine: Inderal LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: Inderal LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. Inderal LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. Inderal is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with Inderal.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or Inderal should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of Inderal therapy. Therefore, when discontinuance of Inderal is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If Inderal therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute Inderal therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD NOT RECEIVE BETA BLOCKERS. Inderal should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Inderal (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta blockers should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid function tests, increasing T₄ and reverse T₃, and decreasing T₃.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case, this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Propranolol should be used with caution in patients with impaired hepatic or renal function. Inderal (propranolol HCl) is not indicated for the treatment of hypertension emergencies.

Beta-adrenergic receptor blockade can cause reduction of intraocular pressure. Patients should be told that Inderal may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if Inderal (propranolol HCl) is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta-blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbital, and rifampin accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and lidocaine have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T₃ concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

PREGNANCY: Pregnancy Category C. Inderal has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. Inderal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: Inderal is excreted in human milk. Caution should be exercised when Inderal is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasisiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctiva reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. Inderal LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from Inderal Tablets to Inderal LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. Inderal LA should not be considered a simple mg-for-mg substitute for Inderal. Inderal LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION — Dosage must be individualized. The usual initial dosage is 80 mg Inderal LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypotensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS — Dosage must be individualized. Starting with 80 mg Inderal LA once daily, dosage should be gradually increased at three- to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE — Dosage must be individualized. The initial oral dose is 80 mg Inderal LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, Inderal LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS — 80-160 mg Inderal LA once daily.

PEDIATRIC DOSAGE — At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Reference:

1. Data on file, Ayerst Laboratories.

D7295/188



PHILADELPHIA, PA 19101

© 1988, Wyeth-Ayerst Laboratories.

Before prescribing, see complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.

Contraindications: There are no known contraindications to the use of Tagamet®.

Precautions: While a weak antiandrogenic effect has been demonstrated in animals, Tagamet® has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity in humans.

In a 24-month toxicity study in rats at dose levels approximately 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving Tagamet®.

Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of Tagamet® HCl (brand of cimetidine hydrochloride) injection by intravenous bolus.

Symptomatic response to Tagamet® therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states have been reported on occasion, predominantly in severely ill patients.

Tagamet® has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when Tagamet® is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either Tagamet® 300 mg. q.i.d. or 800 mg. h.s. concomitantly with a 300 mg. b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.),

demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg. h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. [Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.]

Lack of experience to date precludes recommending Tagamet® for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken in patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: Diarrhea, dizziness, somnolence, headache, rash. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Gynecomastia and reversible impotence in patients with pathological hypersecretory disorders receiving Tagamet®, particularly in high doses, for at least 12 months, have been reported. Reversible alopecia has been reported very rarely. Decreased white blood cell counts in Tagamet®-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and a few cases of aplastic anemia have also been reported. Increased serum transaminase and creatinine, as well as rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including hypersensitivity vasculitis, have been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly un-

likely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving Tagamet® has been reported.

How Supplied: Tablets: 200 mg. tablets in bottles of 100; 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (Intended for institutional use only); 400 mg. tablets in bottles of 60 and Single Unit Packages of 100 (Intended for institutional use only), and 800 mg. Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 (Intended for institutional use only).

Liquid: 300 mg./5 ml., in 8 fl. oz. (237 ml.) amber glass bottles and in single-dose units (300 mg./5 ml.), in packages of 10 (Intended for institutional use only).

Injection:

Vials: 300 mg./2 ml. in single-dose vials, in packages of 10 and 30, and in 8 ml. multiple-dose vials, in packages of 10 and 25.

Prefilled Syringes: 300 mg./2 ml. in single-dose pre-filled disposable syringes.

Plastic Containers: 300 mg. in 50 ml. of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.

ADD-Vantage® Vials: 300 mg./2 ml. in single-dose ADD-Vantage® Vials, in packages of 25.

Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored at controlled room temperature. Brief exposure up to 40°C does not adversely affect the premixed product.

Tagamet® HCl (brand of cimetidine hydrochloride) Injection premixed in single-dose plastic containers is manufactured for SK&F Lab Co. by Travenol Laboratories, Inc., Deerfield, IL 60015.

* ADD-Vantage® is a trademark of Abbott Laboratories.

BRS-TG-L738

Date of issuance Apr. 1987

SK&F LAB CO.

Cidra, P.R. 00639

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In peptic ulcer: RELIEF REASSURANCE REWARD



Tagamet®
brand of cimetidine
First to Heal

You'll both feel good about it.

RESULTS

A better alternative for hypertensives who are going bananas...

Spare your patients the extra cost—
in calories, sodium and dollars.

Spare your patients the rigors of
dietary K⁺ supplementation.

DYAZIDE®

25 mg Hydrochlorothiazide/50 mg Triamterene/SKF

**Effective antihypertensive
therapy...without
the bananas**

DAW

'DYAZIDE' AS WRITTEN.

* Not for initial therapy. See brief summary.

without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of Dyazide is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with Dyazide suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with Dyazide. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin (ACTH)). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency.

Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions.

Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported.

Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine.

Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects

may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components.

Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering

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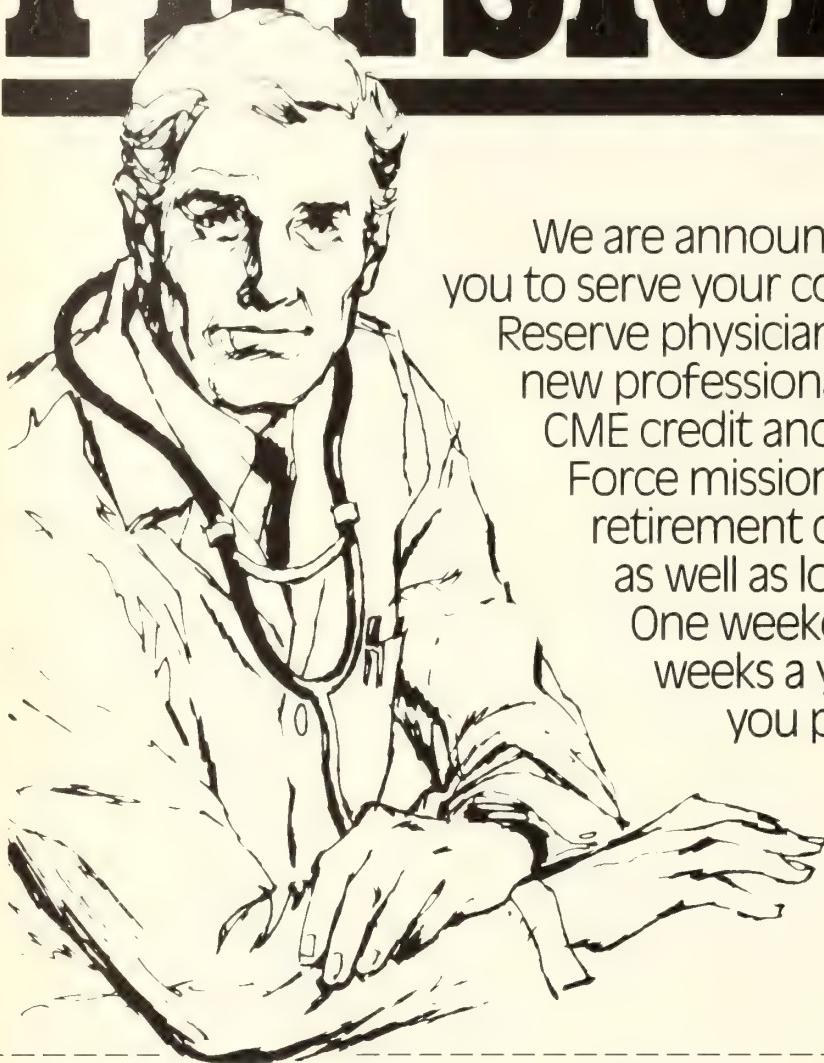
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Cover: Photo courtesy of Mark M. Witoszka, MD. Dr. Witoszka, with two residents, while serving as senior surgeon in the town of Mendi, Papua New Guinea.

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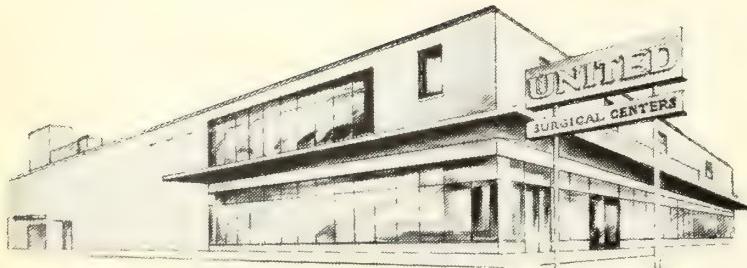
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EDITORIAL

Smoking in Transition

In 1604, not long after Sir Walter Raleigh had introduced tobacco to his native land, King James I spoke words whose prescience would not be fully realized for three-and-a-half centuries: "A custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black, stinking fume thereof, nearest resembling the horrible Stygian Smoke of the pit that is bottomless." When this writer was young, cigarettes were called "coffin nails" by stiff-necked reformers. During World War II the tobacco companies with the cooperation of the armed forces command gave away millions of cartons of cigarettes to "our boys." They were available overseas for as little as 60 cents a carton. It was not until the thirties that the link between smoking and lung cancer began dimly to be perceived. Almost fifty years ago, in 1939, Alton Ochsner of New Orleans and his then student protégé Michael De Bakey first reported the suspected link between smoking and lung cancer. Over the years others have followed in their steps. Evans A. Graham (who himself succumbed to lung cancer), E. Cuyler Hammond, R. Doll of England, and Luther Terry, among others, have played an important role in bringing the dangers of tobacco into the public consciousness. In 1961 Oscar Auerbach of East Orange, New Jersey, a pathologist in the Veterans Administration, published a seminal paper linking cigarette smoking to lung cancer, and also demonstrating the reversibility of the early bronchial changes with the cessation of smoking. In 1986 The Alton Ochsner Foundation presented him with the first

Alton Ochsner Award Relating Smoking and Health. The 1987 award was recently made to Aaron Janoff, PhD of the State University of New York at Stonybrook. Janoff and his colleagues¹ have discovered an enzyme in pulmonary tissue that is altered by smoking, predisposing the victims to pulmonary emphysema. Their research is proceeding along three lines: (1) the effects of cigarette smoking on pulmonary recruitment of elastase-secreting leukocytes, (2) effects of cigarette smoking on the function of elastase inhibitors in the lung, and (3) the effects of smoking on pulmonary elastin synthesis. These studies promise further to elucidate the causation of tobacco-related emphysema.

Despite the stubborn recalcitrance of the tobacco industry, there are many signs of progress. R. J. Reynolds recently absorbed Nabisco, and before that Philip Morris merged with General Foods. American Tobacco has for some time been American Brands. Despite their refusal to admit the dangers of smoking, the tobacco companies have quite clearly hedged their bets in a major way. A patent irony of the present scene is their promotion through their food distributing divisions of the health-giving qualities of some of their products, notably breakfast cereals and low-cholesterol margarine. Nabisco recently canceled a million-dollar advertising campaign for a margarine product after the Academy of Family Physicians insisted that the campaign should include a warning about smoking.

Anti-smoking bills are sprouting up all over the place. The most recent recruit is a New York

City ordinance prohibiting smoking in public places. The armed forces, which used to distribute free cigarettes overseas, now ban smoking in most places. Despite the loss of several recent court cases, the tobacco manufacturer is being assailed by hundreds of other personal injury suits. The betting is that sooner or later in this litigious world they will succumb. When and if that happens a major battle will have been won.

But the war is not over as long as 300,000 Americans die each year of smoking-related diseases.

Seebert J. Goldowsky, MD

Reference

- ¹ Janoff, A: Investigations into the biochemical mechanisms of pulmonary emphysema: Effects of cigarette smoking on enzymes and anti-enzymes in the lung. *Respiration* 50:suppl. 1, pp. 13-25 (1986).

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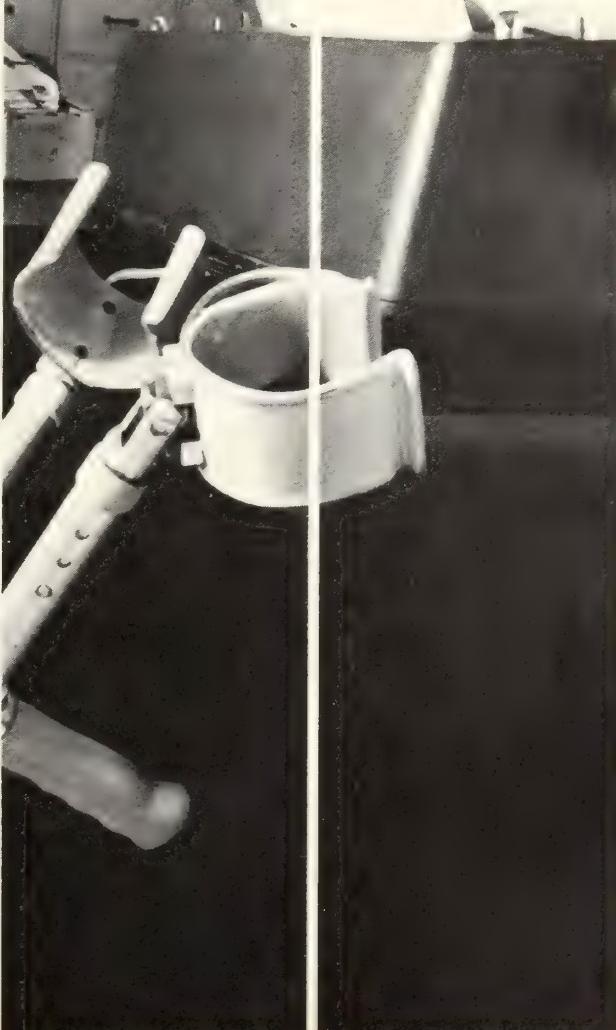
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Historical Note

Reminiscences of an Octogenarian

Jesse P. Eddy, III, MD

It is with true humility and some elements of embarrassment that I stand before you now and think to myself, "What have I done to deserve such treatment?" Before I start to justify to myself the acceptance of such an award, I find it is already an accomplished fact — *fait accompli*, don't you know — and it is appropriate for me to thank you for the honor. I am moved very much by the thought that I may have contributed to the advancement of medical education in Rhode Island, directly or indirectly. I must say I haven't given it much thought, as such, in the usual sense of the word. Both Doctor Julius Stoll and I are highly honored that you are all present this evening, and for this occasion, and we thank Brown University from the bottom of our hearts.

As one who has been retired from active practice in surgery for the past six years, I have not been active in the teaching of clinical surgery of recent date, and, as I look back over my career and review its educational aspects, I think that the best I can do is to hit a few of the high spots that went to make up some of the more important contributions I might have made in the years 1934-1984.

Jesse P. Eddy, III, MD is Consulting Surgeon at Rhode Island, Pawtucket Memorial, and The Miriam Hospitals.

Read at the Eleventh Annual Recognition Dinner on December 2, 1987 for "Distinguished Service to Medicine." The award was presented to Doctor Eddy by the Brown University Division of Biology and Medicine in recognition of his "advocacy for medical education, especially among the physicians in the Blackstone Valley, and of your generous financial support."

When I first returned to Providence in July 1934, following a surgical training on the 2nd (Cornell) Division of Bellevue Hospital, New York City, I was a green, young, surgical intern who was about to associate himself with his father-in-law [Doctor Arthur T. Jones] in the practice of surgery. This has its advantages and disadvantages. Surgical training in those days in New York consisted of a two-year surgical internship, followed in some instances by a one-year surgical residency or one or more years of preceptor-like training with an outstanding surgeon in his private practice. I chose the latter and Doctor Jones, my good father-in-law, had to put up with me.

In those days it was difficult to get a practice started, especially a surgical practice, and I had been away for six years, more or less forgotten. The Rhode Island Hospital was the first to appoint me to the outpatient department as a surgical extern. The Pawtucket Memorial Hospital followed closely with a temporary outpatient department appointment in urology — but then they really did me a favor. They made me the hospital transfusionist. I think it was the only hospital in the state with such an appointment. For administrative purposes, fortunately for me, it was set up in the department of pathology in the summer of 1934. Doctor John Francis Kenney was pathologist-in-chief — also physician-in-chief.

Blood transfusion was a rarity in Rhode Island at the time. I looked up the figures for the Rhode Island and Memorial Hospitals and found, to my utter amazement, that in 1933 the Rhode Island had performed 12 blood transfusions and the Memorial three, in each instance the largest number that had ever been performed by either hospital in a given year. The first task before me was to establish a source of blood, and with the

cooperation of the police and fire departments of Pawtucket I was enabled to address the roll calls at the various station houses, explain that the hospital was looking for donors, and that we were prepared to pay \$40 a pint for blood. They would be examined and their blood would be tested and typed. These officers volunteered for a fee and provided a reliable substantial source of good blood that was necessary when family or friendly donors were not available. The first year we gave 25 transfusions, the next year 50, and the following year 75. In 1939, we opened the first blood bank in the state. Today the Memorial Hospital is averaging 15 to 24 transfusions daily and the Rhode Island Hospital 40 to 60 transfusions a day, roughly a more than 1000 per cent increase in the delivery of blood products.

For the first five years the blood was given directly, fresh from the donor to patient, with no medications added. The process took anywhere from 4½ to 7½ minutes on the average, and an intern always assisted at the process, thus making it educational in the best sense of the word.

Sad indeed is the place where humor never strikes a spark, and there is no humor as funny as a true story — which brings me to an incident that occurred in the surgical outpatient department at the Rhode Island Hospital. It was a busy day, and the nurses were all occupied. Two female patients were in an examining room divided by a sheet on a wire. I picked up a history card and called her name, "Mrs. Tisch." A lady nodded. The card indicated that she had a tumor of her breast. I said, "The nurses are busy right now, and would you be kind enough to arrange yourself so I can examine you. I shall return in a few minutes with a nurse." She again nodded. In five minutes I returned, and she hadn't made a move. I spoke a little more loudly, "Please sit on the edge of the table and strip to the waist, and I shall be back shortly." She nodded. When I returned she was sitting on the edge of the table, stripped to the waist, her hat still on, a feather gracing its crown. This was the first breast case I had seen since leaving New York. I remembered the words of Doctor James Ewing, famed pathologist and director of the Memorial Hospital for Cancer in New York: "When examining the breasts, first look at them, see if they look normal, that one is not larger than the other, that one is not more irregular, does not have a different color — in other words, is dissimilar to the other." There appeared to be no difference. Then he said, "Lift them up, weigh them, palpate

them, see if they are both equally smooth and soft, whether any lumps can be felt. Are they of equal temperature?" All these investigations proved negative, and I said, "Where is your trouble?" She replied, "I have piles, Doctor!" It turned out she was deaf and answered to the wrong name! It was I who was being educated!

It was in the spring of 1950 or 1951 that I traveled to New York City to a meeting of the Cornell Medical College Alumni Association. In 1947, Doctor Charles Bailey of Philadelphia had performed the first successful intracardiac operation ever done in the world on a patient with mitral stenosis, a finger dilatation or fracture of the mitral valve, and the patient had survived! This was a *world record*, the first in the world, although it had been attempted many times since 1900, always with failure. This was the true dawn of heart surgery and created much excitement throughout the surgical world. Doctor Dwight Harken of the Peter Bent Brigham Hospital in Boston was close upon his heels with a similar successful case, done independently. The two disputed who was first for quite a number of years, but Doctor Harris Schumaker tells me it was Bailey. At that New York meeting, I went to the Cornell Division program at Bellevue because Larry Miscall, my good friend who was resident on the 2nd Cornell Surgical Division at Bellevue when I was house surgeon, was presenting several cases of mitral commissurotomy, and I wanted to see them and him. I was thrilled by the success of my friend and for these patients and asked him if he thought I could do likewise. He spoke in the affirmative and offered to send me some of the sparse literature and suggested I visit Doctor Bailey in Philadelphia. Larry also told me that if I found a patient for whom this type of surgical procedure was indicated, he would come to Rhode Island and lend me a hand. I did visit both Doctors Bailey and Miscall in their respective operating rooms several times, and then, lo and behold! Doctor Kieran W. Hennessey of Pawtucket referred to me a patient with mitral stenosis! I referred the patient, Andrew Wright, to Doctor Henry L. C. Weyler, a leading cardiologist in Providence at the time. He confirmed the diagnosis and agreed to the therapy. Accordingly, my friend came up from New York and stood by in the operating room while Doctor Henry Hanley, my assistant, and I performed the first intracardiac operation in Rhode Island on July 21, 1951. The patient made a good recovery and lived until 1974. I did some 25 cases, plus or minus, with one accidental death; but then, as

cardiopulmonary bypass was coming into the picture involving cardiac arrest and other advances, I ceased doing heart surgery. This small effort, however, stimulated other hospitals to take up the cudgel. In a short time the Rhode Island Hospital was bringing Doctor Harken from Boston to do cases with Doctor Murray Beardsley. And it wasn't long before Doctor Lester Vargas, the first Rhode Islander to be formally trained in heart surgery, returned from New York, and a new glorious era commenced.

I have always been interested in the history of medicine, in its accuracy, in its truth, in its ever-forward progress. There has to be a first time for every procedure. Even Adam and Eve will attest to that! There always has to be a first time for every surgeon, for every procedure he performs, or does not perform. This is the joy and privilege of medicine, with the help of nurses and loyal patients. The program of medicine at Brown University is on the high road!

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Surgical Experience in Papua New Guinea

Mark M. Witoszka, MD

I recently returned from Papua New Guinea (PNG), where I served as a surgeon in a remote part of the Southern Highlands Province (SHP). New Guinea is the second largest island in the world, located barely south of the equator to the north of Australia. It is the last of the string of islands spreading down from southeast Asia into the Pacific and really forms a transition zone between the two areas. The island, of which PNG is a part, is known as New Guinea. PNG makes up only part of it. The western half of New Guinea is the Indonesian province of Irian Jaya. Additionally there is a collection of smaller islands around the main land mass. To the north Manus, New Ireland, and New Britain are all provinces of PNG. Also the eastern islands in Milne Bay and the North Solomons group belong to PNG. PNG is truly the last unknown and virtually the least inhabited place on the earth to be explored by Europeans, and even today some parts of the country have made only the minutest contact with the west.

I was employed by the independent government of PNG as a senior surgeon in a base hospital of 200 beds located in the small town of Mendi in the SHP, which serves a population of approximately 250,000 people. Within a 26,600 square km area of the province there are 16 main ethnic groups occupying highland grass-floored valleys and basins between the altitudes of 2000 and 7000 feet. The total number of tribes with

their own independent languages in the entire island is counted by anthropologists at 700. This hospital of 200 beds was built about 10 years ago by the Army Engineering Corps of Australia. The hospital has four wards plus 20 beds in full nursing care which served as an intensive care unit and also provided postoperative care. The four wards included a pediatric ward, internal medicine ward, obstetrics-gynecology ward, and my surgical ward, each consisting of 50 beds. There were two reasonably well-equipped operating rooms with two modern German autoclaves for sterilization, two Draeger-type anaesthesia machines equipped with Fluoton, relatively modern anaesthesia facilities. The hospital also had a well-equipped pharmacy with ample supplies of antibiotics (chloramphenicol, penicillin, Gentomycin, Keflex, Bactrim, chloroquine, Flagyl), and nearly all intravenous solutions except TPN (total parenteral nutrition). In the operating room there was an ample number of instruments with sets for urological procedures, including a German cystoscope, sets for orthopedic, gynecological, and abdominal surgery, as well as principal sets for craniotomies, mostly for burr holes and decompression. There were also old, but sufficient instruments for the treatment of eye trauma, ear, nose, and throat emergency procedures, as well as a flexible esophagoscope and a sigmoidoscope which never worked! The most important equipment for me was an excellent electrocautery machine, which was most useful. I used this exclusively as a diathermy as well as an electric knife (it worked very well and never failed). Operating room lamps were sufficient when working, but we had frequent light failures, due to faulty bulbs, as well as blackouts. These occurred quite frequently (4-5 times a week), and occasionally I had to finish surgery with a hand-held flashlight!

Mark M. Witoszka, MD is consulting surgeon for the Adult Correctional Institute (ACI), Cranston, Rhode Island, associate staff with the Department of Surgery at The Miriam Hospital, and continues in private practice in Providence, Rhode Island.



One of the five units of the Mendi Hospital, Papua New Guinea.

The hospital was in a pleasant location, uphill from the small town, approximately three miles from the airstrip. We had an emergency generator in case of power-supply failure (there was a turbo dam near Mt Hagen). There was also a wide field for landing of helicopters delivering emergency cases from remote parts of the province. The helicopter would bring patients approximately once or twice a week, which was an expensive proposition costing the government about \$700 for each delivery. The hospital had an administrative staff consisting of the hospital secretary and his administrative staff and a record room with records and data for each patient. The hospital medical staff consisted of four physicians: one medical superintendent who did a lot of obstetrics and gynecological work, a general medicine physician, and two of us as specialists — one pediatrician (a lady doctor from England) and myself as surgeon. There was also another physician who held an administrative position for the Provincial Health Department, but who would also participate in coverage of night duties. All of us had to share in the general night duties, approximately once or twice a week. Of course, being the first surgeon in this hospital, I was on duty practically all the time, because, if any emergency surgery was needed during the night, I was called to the hospital for advice and eventually had to operate. In some cases I tried to teach my colleagues some emergency procedures.

I would perform all varieties of surgical procedures from frequent Caesarian sections, urological cases (mostly prostatectomies and urological trauma), orthopedic procedures (of course,

mostly fractures, often very complicated requiring plates and wiring), plastic surgery (mostly for severe postburn contractures, particularly in small children), and very frequently treatment of severe burns due to falling into open fires in the huts. I frequently treated trauma to the eyes, mostly repair of the vitreous body, and of course performed a wide spectrum of general surgical procedures on adults and children, even newborns, which required emergency treatment of congenital malformations. The most common procedures in children were for intussusception and "pig-belly" (see below). In adults, the most common procedures were laparotomies for duodenal peptic ulcers, bleeding (patient walking to the hospital with a hemoglobin of $3\frac{1}{2}$ to 4 grams), perforations, intestinal obstructions due to tumors and torsion, various neoplasms and hernias, giant Baker cysts, amoebic necrotizing colitis, and amoebic liver abscesses. On several occasions I drained liver abscesses very successfully in spite of the general attitude favoring medical treatment.



"Pig-belly" bowel with necrosis.

One of the most fascinating surgical pathological conditions seen in the highlands of PNG was "pig-belly." "Pig-belly" is necrotizing enteritis of the bowel. It was the commonest cause of an acute abdomen in surgical practice in highland hospitals, seen in my practice quite frequently at the rate of one case per week, particularly in children. Only a few years ago, it accounted for 24 per cent of deaths in children from 1 to 15 years of age and was also the most frequent cause

of death in children over the age of one. This disorder is very specific and unique for PNG. It is a fascinating ecological story in which man, the environment, diet, and the domestic pig all play significant interacting roles. "Pig-belly" occurs after a sudden influx of great amounts of proteins, namely pig meat, consumed after prolonged periods of deprivation. This sudden dietary change caused by eating pork leads to a proliferation of clostridial organisms in the intestine which sets in motion a train of events which may lead to intestinal gangrene and death. On autopsy, generalized inflammation and patchy gangrene of the small intestine was seen. The mucosa was necrotic and showed areas of ulceration. Several of these individual lesions were confluent, forming loops of necrotic bowel which were purple-black, sausage-like, and grossly distended. Bacteriological examination of the intestinal contents of patients with "pig-belly" showed that *Clostridium perfringens* type C strains, which produce betatoxin, were associated with the disease. And, of course, early surgical intervention was crucial to save the lives of the patients.

One of my most exciting experiences in Mendi Hospital concerned a patient delivered by helicopter from a nearby tribal war fight with an arrow protruding from his anterior lateral chest. I explored him successfully, extracting the arrow, which was perforating the lung and left ventricle. The patient survived the surgery, but eventually died from lack of postoperative care. This was one of my first cases after arrival in PNG, and afterwards I experienced many arrow wounds at the rate of at least three to four a week. Overall, I was surprised how little unnecessary surgery was performed (four cases in approximately 300 major cases). We had very limited diagnostic tools, including portable x-ray, hematology, differential Gramstain, and very limited cultures. The most important tool we had was ultrasound. Our great little machine was new and worked well. With it we could even diagnose hepatomas, a frequent occurrence in our hospital. Lastly, I must mention giant melanomas, which is another of the fascinating diseases in PNG.

My weekly routine consisted of surgical rounds three times a week with residents, nurses, physical therapist, and student nurses, occasionally including guests from overseas or other health facilities in PNG. Surgical rounds were of the old-fashioned type, visiting each individual patient in the surgical ward, reevaluating their condition and planning treatment. Wound dressings were



Common size of melanoma in Papua New Guinea.

performed at the bedside. The average room in the ward had approximately 10 beds, most of the beds without mattresses, only plywood platforms covered by bamboo mats. The patients were dressed in their own clothing, which meant mostly no clothing except for an apron covering the genitalia and buttocks, made of so-called tanget grass. The children were nude. Practically all patients were accompanied by family members. Officially only two family members were permitted per patient. They usually stayed under the bed or together with the patient. Frequently it was difficult to distinguish who was the patient and who was the family member. During the night the temperature dropped usually to about 50°F. Therefore, after surgical rounds, the patients would dry and warm themselves in the sunny courtyards. I operated five days a week for elective surgery and performed emergency surgery any time it was required.

Besides surgery, surgical rounds, diagnostic procedures, and consultations in other wards, I participated as much as possible in the outpatient service, which was swamped with patients. Not infrequently I would see, between my surgical cases, 30 or 40 patients for a quick diagnosis or advice. I averaged three to four major cases a day with numerous small cases such as fractures, trauma to the eye, and an incredible number of drainages of abscesses from pyomyositis, and splinters and infections of the feet. Many abscesses were drained by the operating room staff



PNG trained Intensive Care Unit (ICU) recovery room staff.

technicians, who were trained to do the procedure. Once or twice a month I would visit remote medical centers for consultations as well as treatment of numerous patients who were handled there by Health Extension Medical Officers (HEMO), or missionary-trained nurses. It was a very busy time, but very rewarding and often exciting when a helicopter or small plane brought us injured patients from the frequent ongoing tribal wars in our Province. Arrows through the chest piercing the lungs, heart, and abdominal organs sometimes required really fast action, which I was able to handle with my training in cardiovascular surgery and with the help of my own modern set of instruments. Fortunately, one thing we did not lack was blood, which was happily donated by family members.

The health service structure in PNG was quite efficient, consisting of two suppliers: 1) the PNG government, and 2) various missionary agencies. The country with a total population of 3 million is divided into 17 provinces, each province having an independent health maintenance organization responsible for the health care of that particular province. Most of the provinces have a hospital with satellite medical centers in the rural areas. Medical centers have their own posts, which are the last link of the health care. The medical centers have HEMOs who supervise several nurses and provide primary care services. The posts are served by native individuals trained

in giving first aid. In some of these medical centers there is radio communication, or 4-wheel drive roads, or an airstrip facilitating the transport of seriously ill patients to the hospital. Medical centers organized by the United Church or Catholic Mission provide particularly excellent services.

Surgery serves an important role in the medical services in PNG, particularly due to the large number of injuries caused by living in the remote tropical forest, by tribal wars, and by increasing numbers of motor vehicle accidents. But the most important health problems in PNG are: epidemic malaria as number one, pulmonary infections, filariasis, amoebic diseases, leprosy, venereal diseases, and diarrhoeal diseases, as well as an increasing incidence of tuberculosis (TB). TB is of great concern since there has been a steady increase in new cases detected since 1976, and the incidence of TB nearly doubled since 1976. The data for leprosy are more encouraging, since the incidence and prevalence rates have remained unchanged over the last 15 years. The prevalence rate has remained steady at 2.8/1000 and the incidence rate at 0.26/1000. In 1982, for example, there were 8,455 cases. Venereal disease figures are alarming. The incidence for gonorrhoea in 1980 was 36/10,000, and an increase in incidence of 70 per cent over a 5-year period is noted. For syphilis the incidence was 15/10,000 in 1980, increasing to 22/10,000 in 1984.

Malaria is currently the second commonest cause of morbidity and mortality in PNG, second only to pneumonia. In the period 1980 to 1984, it accounted for 11 per cent of all admissions with an 8 per cent mortality. The incidence of malaria began to increase in the mid 1970s, which prompted a recommendation for change of strategy for malaria-control programs. In 1975, spraying was limited to areas of economic importance. Unfortunately this reduced coverage by 50 per cent. By 1979, the incidence was equal to that noted in the 1950s. The annual parasite rate among children less than 10 years old in indicator villages was 30 per cent between 1970 and 1984. The Plasmodium falciparum (PF) malaria infections increased from 48 per cent to more than 70 per cent for the same period. At the same time chloroquine resistance PF has emerged. This is widespread throughout all island provinces and all mainland provinces. In-vivo resistant rates range from 8 per cent in Kiumga to 100 per cent in Popondetta between 1979 and 1983.

As prevention is better than cure, a lot of

money, time, and effort needs to be diverted to a health awareness campaign. TB, leprosy, malaria, and venereal and diarrhoeal diseases should involve community education and participation in their control. The United States as a leading country in the world of sophisticated medical health service should participate and help, particularly in education in these areas.

PNG has a new medical school in Port Moresby, which graduates about 25 doctors a year. Last year, the first professor of surgery was appointed, Doctor Frank Smith, who has already spent nearly 30 years working as a surgeon in the country. He and Doctor Kenneth Clezy are the most experienced surgeons in PNG, where they devoted most of their lives working and serving needy people. Their skill and expertise was astonishing, and the quality of work excellent in all fields of surgery. I was glad to have their support and advice as experienced tropical surgeons. I was happy to train two local residents, particularly Tom Yambai from the Sepik River, an extremely intelligent and skilled physician. Visiting remote medical centers in the rural areas of the country gave me the opportunity to explore, to participate in unrehearsed and primitive ceremonies of pig killings, to watch fascinating and exotic "sing-sing" dancing, and to experience the life of the bush people in the villages. It was a wonderful experience to work with the native people, particularly those from the bush where life has not changed much for the last several thousand years, and to have had the

privilege of living in an unspoiled and unpolluted tropical country.

In summary, I enjoyed tremendously the opportunity to serve the people in this fascinating and beautiful country, to which I hope to return some day. I would be happy to share my experiences and discuss them with any who are interested in similar work in the future.

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"Sing-sing" dancing ceremony in Papua New Guinea.

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The Anatomy of an Experiment — The Rhode Island Hospital and the Colonel Rice Mission

Informed Consent in Those Days Was Unheard Of

John S. Dziob, MD

Prologue

Pearl Harbor, December 7, 1941! The Japanese virtually wipe out the United States fleet. "In-famy," cries President Roosevelt, and America is in World War II up to its ears. The Giant among the nations of the world was caught napping, but not for long. Once aroused, chagrined and angry, the country mobilized in earnest. Along with the physicians nation wide, the Rhode Island Hospital responded. Many of its staff enlisted in the various branches of the military.

In this paper we are mainly concerned with the fortunes of Rhode Island Hospital's Evacuation Unit — the 48th Evacuation Hospital — and more specifically with the adventures of a small group of its doctors and enlisted personnel who volunteered in the early months of 1943 in Assam, India to form the nucleus of the Colonel Rice Mission in the China-Burma-India (CBI) Theater. This mission was designed to test sulfa-mefazine in the field as a prophylactic agent against falciparum (malignant tertian) malaria. In the words of Lord Mountbatten, it was "causing more casualties than bullets."¹ The mission was presented to the volunteers as "top secret, arduous, and hazardous." Some choice!

This scenario took place in the northeastern corner of Assam, India, the spot, Margherita, a native jungle village in the foothills of the Himalayas, and the time, the early months of 1943.

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How We Got There

Let us start at the beginning. The Unit in Providence, Rhode Island was formed of volunteers — doctors, nurses, and enlisted personnel of the Rhode Island Hospital. It was activated as the 48th Evacuation Hospital on August 17, 1942 under the command of Colonel William Mahoney. It was sent to Fort Devens, Massachusetts, indoctrinated there in military ways, and acquired Colonel Charles Leedham as its commanding officer, an army career doctor, along with several more doctors — Lieutenant Colonel Abraham J. Meister, Captain Isadore Garber, Captain Edward Greuninger — and also more nurses and enlisted men, none of the latter being Rhode Islanders.

We marched and played at Fort Devens at being army for approximately six weeks, and then the Unit was off to Murphreesboro, Tennessee for battle maneuvers, returning to Fort Devens for the Thanksgiving holidays.

It seems as though someone or Fate was very anxious to get us into the fray without further delay, for shortly after the Christmas holidays, the 48th Evacuation Hospital was on a troop train crossing the country to Camp Anza, a staging area in Southern California.

After vaccinations, injections, more drills, and marches over the rolling hills and vineyards in the area, lo and behold! We were trudging up the gang plank of a converted Italian luxury liner. It then steamed out of the Port of Long Beach, California with a plane escort which stayed only long enough for us to clear the waters about the harbor. Thereafter, it was solo without any type of escort southwestward on the Pacific Ocean. Destination? A secret.

This lonely vessel with its precious human cargo

zig-zagged for one month ever southwestward, logging 6900 miles without incident — no hunting, stalking Nazi submarines, nor that infamous terror of the seas, the Nazi battleship, the *Graf Spee*. There were several false alarms with their calls to battle stations. Small comfort indeed. On that vast expanse of ocean under a moon — and star-lit sky, the blacked-out ship would still stand starkly outlined against the horizon. Snap your cigarette lighter while on deck at night and you faced instant court-martial. (We all smoked then!) That little flicker of light was all a searching submarine needed to spot and sink us. What a prize it would have been for them — one general hospital unit, three evacuation hospital units, one medical battalion, units of the Corps of Engineers coming off the famed Alaskan Highway, plus a ship full of enlisted personnel.

Week after week at sea followed, across the Equator, then the International Date Line, more weeks, and finally, after logging 6919 miles, we set foot in Wellington, New Zealand. After three days of shore leave in the capital of New Zealand, we were back on the ship for another trip of 2916 miles through the Tasmanian Sea and the Indian Ocean to Perth, Australia, where after two days of shore leave, we were out again across the Indian Ocean and the Arabian Sea for the completion of another 4493 miles to Bombay, India. The journey took approximately six weeks — Long Beach to Bombay.

After all of the oceans and seas, we were allowed ten days of acclimatization at a British camp at Dea Lalli, outside of Bombay. While there, in addition to getting used to the climate, we were instructed in the diseases endemic to India. So after all of these weeks from Long Beach, California to Bombay, India, a total of 14,000 miles, one would think that we had reached our destination. But, No. It appeared that we would still have to traverse the Subcontinent of India, approximately 1000 miles more.

The journey across India by means of a narrow-gage railroad ought to have been a tourist's delight. Well, hardly. As the miles dropped away and the nurses, the doctors, and the enlisted men began to get the feel of India at the numerous stops, some would jump off to "puke their guts out," others to stand dumbly sweating and shaking with the chills of malaria, while still others would be closeted with bloody dysentery. The rest of us just stood by commiserating and each dreading his own turn.

At Howrah on the east coast above Calcutta, a river port, we boarded a side-wheeler, com-

parable to the old Mississippi steamers. This vessel slowly but steadily splashed its way up the Bramaputra River for another 400 miles to Dibrugarh in the northeast corner of Assam. Here a transfer to the narrow-gage railroad cars for a trip of about 80 miles to a partially hacked-out area of jungle at Margherita. At last, this was the destination — a point 15,650 miles from Long Beach, California, — 18,650 miles from New England.

Flash Backs

In thinking about this peregrination, 44 years ago, some things still pop into the foreground:

1. At Murphreesboro, Tennessee, the autopsied, broken bodies of the tank crew that had fallen off a bridge — all their long bones crackling like bean bags when lifted.
2. The exhilarating beauty of the freshly-breaking dawn over the desert against the background of misty mountains, etched on the horizon somewhere in the West.
3. Trudging up the gangway of the troopship in Long Beach Harbor, California.
4. The dreaded moonlit nights in crossing the Pacific Ocean, that exposed the ship to possible enemy submarines, and the sickening, sinking sensation at a sudden shrieking of the alarm horn, sending the ship's crew frantically to battle stations.
5. The Colonel Isidore Ravdin medical lectures on board ship, he of the University of Pennsylvania Unit.
6. Crossing the Equator, and the traditional hijinks of the crew.
7. The first view of the "Southern Cross" in the bejeweled sky.
8. The barmaids in a pub in Wellington, New Zealand expertly sending the foam-bedeviled brew sliding smoothly down the length of the long crowded bar.
9. The handsome blond Viking-type male leaning languidly against the ship's spar on deck, sharpening a long wicked-looking knife for the benefit of the nurses and his own ego.
10. The two-foot long earth worms at the British Camp outside of Bombay.
11. The trek across India in narrow-gage railroad cars with our personnel puking, diarrheastricken, and shaking with high fever malaria at the many stops.
12. The sidewheeler boat on the 1800-mile-long Brahmaputra River, India's Mississippi, with its giant cockroaches.
13. And the first night at Margherita, alive with

the shrill, buzz-saw, pulsating cacaphony of the jungle's insect world.

How It Came About

Now that we were there, what did we do? Jump right in treating battle casualties? Absurd! For several weeks, nothing but fighting the jungle. Of the four medical outfits clustered around Ledo, only the University of Pennsylvania General Hospital (the 20th General Hospital) cared for patients. There were casualties, but not battle casualties, from the Chinese and American engineering outfits building a road from Ledo, Assam over mountains and through jungle to connect up with the old Burma Road, which currently was in the hands of the Japanese.

General "Vinegar Joe" Stillwell had suffered a humiliating defeat in Burma. His shattered army struggled through the jungle and over the mountains to a haven in India. Here Stillwell had regrouped and replenished his forces, both human and material, ready to launch a counter-campaign, as soon as Ledo Road became a passable reality. A road was the primary objective, the highest priority, a road which would support small tanks and which the General, supported by the Air Force, could use to drive the enemy out of Burma and connect up with the Old Burma Road. It had been started by the British with little success. They had turned it over to the Americans some months before we arrived in Assam in December 1942.

So we waited along with the other two evacuation hospitals fighting the jungle, living in bamboo bashas co-inhabited by vermin in the grass thatched roofs, giant blood suckers, horned toads, scorpions, mosquitoes, and snakes; sleeping on canvas cots under mosquito netting; eating spam, spam, spam; hating the distasteful routine trips to the latrine; not a day going by without someone clubbing a cobra to death alongside the pathways to the mess hall; awakened at dawn by hordes of screaming monkeys swinging through the giant tree tops, making further sleep impossible. The ennui was making everyone irritable. Several of our older officers conspired to have themselves sent back to the States.

Colonel Leedham, our commanding officer, took advantage of an opportunity to transfer the 48th Evacuation Hospital out of the jungle to Rangarh and civilization, there to run a station hospital. Good news? Not for everyone. The 48th Evacuation Hospital was too large for the table of organization of the station hospital. Therefore the colonel and his staff trimmed the unit down



Standing on the Burma border into China. Left to right: Irving Beck, John Dziob, unidentified.

to size by discarding the excess number of male officers and enlisted men. The discards would be on detached service in Margherita, relegated to a "pool," the members of which would be at the mercy and whims of the "Brass" at Ledo.

The discards were unhappy, mighty unhappy. For them the prospects of practicing their kind of medicine seemed pretty remote indeed. Added to that was the fear of being shuffled around and becoming lost from the parent unit for the duration. To show that they were concerned at the fate of the contingent being left behind, the colonel and his staff had secured for us the opportunity to volunteer for a mission, which they could

only characterize as "Top secret, arduous, and hazardous" — a Hobson's choice! At the words, "Top Secret," I shuddered. They brought up visions, not of "sugar plums," but of a diabolical Japanese shoving long slender slivers of bamboo under my finger nails. I'm not a hero, but, somehow, I shakily raised my hand. I looked around to see who of my comrades had responded to the offer. I saw the hands of Captains Irving Beck, Edward Greuninger, Isadore Garber, William Leet, and Frederick Webster, of Lieutenant Milton Korb, and one other, and that was it. Major Eric Stone had already declined to leave with the Ramgarh group, preferring to remain behind with the discards. Along with Major Stone, we were to meet with the Top Brass in the next few days for indoctrination.

The Mission

At headquarters in Ledo, a week or so later, the seven volunteers, after being sworn to secrecy, learned that we should be under the command of Colonel Earl M. Rice, an expert malarialogist; that in the official records the mission was listed under the code name "MARY," a study in nutrition, but that actually it would test in the field the efficacy of the experimental drug sulfamerazine as prophylaxis against malaria, the control of which was of such vital importance to the Allied Forces in the CBI Theater. Atabrine (quinactine), a German product, was in short supply.

It was a relief to me that we would not be penetrating the enemy lines. Yet, it was somewhat disconcerting to realize that, instead of injecting guinea pigs or white mice, we were to become the experimental animals for the mosquito. Instead of our doing the injecting in a laboratory, the Anopheles mosquito would do the injecting into our bodies in its own habitat — an area having the highest incidence of malaria in India and perhaps in the world. I could see why they termed it "hazardous" — a sure-fire opportunity to acquire cerebral malaria, 100 per cent fatal.⁵

The Setup

Another hazardous aspect was the locale in which the experiment would take place — the bamboo motor pool at Dum Duma, near Hansara, Assam, compounded by the onset of the monsoon season (June-September). The experiment was to be conducted by two groups — the first, American; the second, Chinese. The latter were our allies, and their inclusion would have good political and propaganda value. Each contingent was to be se-



Left to right: Hubert Holdsworth, John Dziob, Melvyn Douglas, unidentified, Isadore Garber. At Ledo Road, Burma, 1944.

questered in a separate area — the Americans at Dum Duma, the Chinese about 10 miles up the burgeoning Ledo Road.

Why were the Americans at Dum Duma? We were soon to find out. It became obvious that only the Americans or the British would have tolerated the first choice. The Chinese without a doubt would have rebelled at the prospects and quit. To paraphrase Noel Coward's song, "Mad Dogs and Englishmen," only mad dogs and Americans go out in the noon-day sun and slime of the bamboo grove and carry out the task with a modicum of aplomb and fortitude.²

To prepare us for this undertaking, Colonel Rice and his native doctor friend accompanied Captains Beck, Dziob, and Leet into a native village to see cases of malaria and to familiarize themselves with slides of the malarial parasite. The village consisted of a cluster of mud walled-huts with grass-thatched roofs, a few goats, and a scattering of livestock. The hospital occupied one end of the compound, a single large basha with cots lining the walls. Each cot had a native

woman cradling her naked offspring in her arms. The Hindu doctor explained that they delivered babies by the sense of touch, because the genitals of the female were sacrosanct and not to be viewed, even by the physician. He worked with his hands under the sheet covering the whole lower abdomen-genital area.

Finally, all preparations having been completed, the American Unit took off in trucks for Dum Duma, near Hansara, India — our home for six weeks. Our personnel consisted of Captains Dziob and Greuninger and Lieutenant Korb of the 48th Evacuation Hospital, the captains from a Medical Battalion and from a Quartermaster's Company, along with the enlisted men under their direction — 200 in all. Captain Dziob was to serve as commander over-all. Captain Beck was our laboratory man, coming out of Margherita at intervals to take blood smears of men who had developed fever and arrange for their transfer to the 20th General Hospital at Ledo if the smears showed the malarial parasite.

I was instructed to overlook breaches in the routine protective measures by the soldiers, such as, failure to apply antimosquito lotion, failure to tuck pant legs into stockings, failure to keep collars buttoned about the neck, and failure to secure mosquito netting over the canvas cots. The objective was to encourage the mosquito to bite. We set up our post in pyramidal tents. Unfortunately, the monsoon rains came early. It rained every day, and several times a day, but brought no relief from the enervating heat and humidity. Clothes had no time to dry; we had to put up with damp uniforms.

For six weeks we lived in misery. The bamboo grove covered a large area. The trees, tall and slender, were closely packed in rows, capturing and maintaining the moisture in the ground, cutting down on the sunlight filtering through when it was not raining. The combination of little sun and daily rain turned the whole camp into a gigantic bog. At night, with the wind and rain swaying the treetops against each other, their hollow trunks clacked with the resounding cracks of pistol shots.

I saw no cobras. Really, no self-respecting cobra would be caught dead in the mud, but there were other nasty vermin. There was no letup in the rains. The trucks that brought in supplies sank to their hubs in the mud. The latrine facilities became horrendous. Their contents would float up to the rims of the seats. Maggots writhed in bunches. The black widow spider lurked there, waiting to strike the plump and juicy hind quar-

ters of the well-fed Americans rather than the dessicated rumps of Hindu coolies. No sooner were they cleaned out, then the latrine trenches would refill in a day or two. It was a losing battle. So most of the time, one would have to climb atop the wooden structure of the latrine, crouch down over the hole, and deliver.

I admired our enlisted men. They did not complain. I couldn't help recalling Tennyson's lines: "Theirs not to reason why; theirs but to do or die,"³ and the possibility of the latter in this hell-hole was not a figment of the imagination or an exaggeration. It was real.

Phase A

Prior to leaving for the bamboo motor pool, Colonel Rice spoke to me about sulfamerazine, urging me to take the pill; he said it had been very effective in the laboratory. So I convinced my staff of officers also to use the sulfamerazine. For the next six weeks, each morning before breakfast, the men (200 of them) would line up at parade rest. Then Captain Dziob and his entourage — Captain Greuninger, Lieutenant Korb, and the respective captains of the Medical Battalion and the Quartermaster's Company — would pass along the line. Captain Dziob would place a tablet into the open mouth of each soldier, have him swallow, then stick out his tongue. This maneuver was designed to prevent them from secreting the medication and subsequently spitting it out. One hundred men received the sulfamerazine; the other one hundred, a placebo (sodium bicarbonate, five milligram tablet).

Soon things began to happen. Some of the enlisted men, the "good old GI Joes," began to complain of fever and chills. Captain Beck with his technicians would come in, take blood smears, and arrange, if positive, for the patients to be sent to the 20th General Hospital at Ledo. The mosquitos were having a field day, and malaria among the men was documenting their successes.

Moreover, the constantly high humidity and the miserably tasting, highly chlorinated water from the Lister bags together brought on dehydration, — the former (humidity) by the loss of fluid via the constant sweating, the latter (chlorinated water) by inhibiting any desire to drink. Dehydration was a way of life in this hell-hole. The Black Hole of Calcutta had nothing on us.*

*Black Hole of Calcutta: A dungeon in Calcutta, where on June 29, 1756, one-hundred-twenty-three of one-hundred-forty-six Europeans reputedly died from heat and lack of air. Ref. Webster's New World Dictionary, p. 147.

Unfortunately, by introducing a sulfa drug, another complication was added to the picture — a renal one, ie, flank pain radiating into the groin. We diagnosed renal colic, and had the stricken ones transferred to Ledo. I kept no statistics. That was the prerogative of Colonel Rice, Captain Beck, and Captain Webster. However, I can recall at least a half dozen renal colic cases occurring in a short time in the sulfamerazine group, but none from the placebo group.

At the completion of the six-week period, we had brought Phase A of the experiment to a welcome close. We were now ready for Phase B. This meant transport of our crew to an area outside of Jorhat, Assam, about one-hundred-fifty miles to the southwest — an area diametrically the opposite to that of Dum Duma; namely, one with a drier climate and a very low incidence of malaria. Here we were to live for another six weeks to allow incubation in those of our personnel who were bitten by mosquitos just before moving out.

We anticipated no new infections during Phase B. We had survived the ordeal of the bamboo motor pool, except for the cases of malaria and kidney stones. We were in good shape, having for the most part escaped dysentery and other endemic diseases. Of course, we had courted the malaria.

Phase B

We set up camp on a gentle grassy slope of what looked like, and actually had been, a golf course, near the native village of Dergun. The site was a fairly pleasant one. There was a nearby river from which our water was drawn into a tank truck, boiled, chlorinated, and dispensed in large Lister Bags, hung from several bamboo supports in two or three spots in the camp — our drinking water.

For the first day or two, we were on display, guilty of undue exposure, to the native children of the village, who lined up across the road fascinated at the goings-on of this influx of strange soldiers. We paid them no attention, although it was a little disconcerting to have to void in public into a long temporary trench just off the road. The children actually were far enough away so as to be unable to see any details, other than an arching urinary stream.

Aside from ordinary chores, we had little to do. Captain Greuninger and I made a few trips to a native bazaar, sloshing around in the mud from stall to stall, keeping out of the way of the meandering sacred cows. The latter were privileged, unmolested and free to pick their way

through the crowds. The produce on display was decorated with buzzing flies and insects. The natives — the men clad in their loose, elongated diaper-like trousers (dhotis) and the women in rumpled saris, faces masked except for the eyes — milled around, the men's lips and teeth stained scarlet from betel-nut juice. Everyone seemed to be chewing it. It occurred to me that the dhotis could have been the prototype of the Zoot suits of long ago in the States. We ended up by buying some limes for our "Bull Fighter" whiskey, a periodic ration by the Army. Captain Webster saw to it that we got our share of the allotment.

For a little excitement and to overcome the boredom, several of us drove to a shack in a wooded area away from camp and off limits to the Army, where a creative entrepreneur had built a reputation for excellent chicken dinners — off limits because of the danger of hepatitis and endemic disease. It was a little revolting every day to see the scrawny native pigs with snouts to the ground, gobbling up human excrement and bovine dung as they foraged about the compound. Nothing goes to waste in nature. On the whole, however, the camp at Dergun was a god-send compared to what we had come from in Dum Duma.

The following are some of the highlights at Dergun that come to mind, even after 44 years:

1. The party under the stars with all of the officers seated around a long table, like King Arthur's Knights with smoking flares on poles providing illumination and protection from insects, celebrating the news from Doctor Wilfred Pickles in Providence, Rhode Island, that my son had been born, with the infant and mother doing well. All the Bull Fighter liquor stored in foot lockers was brought out and consumed to the accompaniment of hilarious off-color stories. After Dum Duma we needed something like that.

2. The plight of Captain Greuninger, my tent mate, an affable, corpulent gentleman, groaning on the sleeping cot in the tent from a sprained ankle, incurred leaving the above party and stepping into a gopher-like hole. An injection of morphine provided the needed relief.

3. Captain Garber, at the party, a teetotaler, behaving in as hilarious a manner as the rest of us, probably having got inebriated from the fumes exhaled by his comrades. Needless to say, a smashing time was had by all with Captain Greuninger the only casualty.

4. Then, there is the night that I was awakened by a sudden deluge after midnight (3 a.m.), following a very hot day, to find a small brook rush-

ing through the middle of the tent. It didn't awaken Greuninger. Someone had to cap the vent in that pyramidal tent. Getting out from behind the mosquito netted cot, I stripped off all my clothes and naked went outside, scampered up one corner of the heavy canvas structure, capped the vent easily, and for a moment, like King Kong atop the Empire State Building, giving way to a boyhood suppressed desire, beat my chest and howled like Tarzan in defiance of the turbulent elements; and Greuninger slept through it all.

No further incidents occurred, and at the completion of the six weeks, the trucks appeared, we struck our tents, gathered our gear, and were off back to Margherita to an uncertain future, but with a plan in mind.

Epilogue

In England at the height of the Nazi Blitz, Churchill offered to his people: "Blood, sweat, and tears." In June of 1943, the Top Brass at Ledo, Assam, India, China-Burma-India Theater, World War II offered to the Group of 7, volunteers from the 48th Evacuation Hospital: "A mission tops in secrecy, arduous, and hazardous." The British survived and so did we.

1. Was it top secret? Very much so, for, forty years later in asking the Surgeon General's Office several months ago by telephone from the Rhode Island Medical Society's Library on two separate occasions for a copy of the Colonel Rice Mission Report, I was informed that they had no knowledge of any Colonel Rice Mission. Moreover, Doctor Irving Beck recently under the auspices of a friend, a general in the Army, the latter seeking to obtain the same information, was given the same negative answer.

2. Was it arduous? My answer: Try living for six weeks under the conditions portrayed above, existing at the bamboo motor pool at Dum Duma. The Black Hole of Calcutta had nothing on us.

3. Was it hazardous? My answer: Doctors Irving Beck and Frank B. Cutts in their report of the treatment of falciparum (malignant tertian) malaria in the Chinese at the 48th Evacuation Hospital in Myitkyina, Burma, 1944, show it as having a fatality rate of 100 per cent.⁵ Certainly the volunteers put their lives on the line at Dum Duma.

4. Did we accomplish anything? Yes, we did. It certainly would have been a crime if, after putting 400 human beings (200 Americans and 200 Chinese) at risk, we came up empty-handed. I speak from my own experience with sulfamerazine in the field. I apologize for not having sci-

entific data: I tried to get it. You can't fight "city hall." But I can cite what we lived through:

1. Neither I or any of my officers on suppressive doses of sulfamerazine came down with malaria.

2. None of the enlisted men taking sulfamerazine to my recollection developed malaria. Those sent to the 20th General Hospital in Ledo with malaria came from the placebo group.

3. We showed, too, that sulfamerazine in the tropics with a concomitant dehydration problem was risky from the standpoint of generating kidney stones and colic. Fortunately, in the spring of 1944, Atabrine became available in the CBI Theater and became the drug of choice.

Finally, one thing of which we were proud came out of Fate's having thrown the Group of 7 together for three months at Dum Duma and Der-gung: The realization that together we were equipped to run a small hospital at Tincha, in virgin jungle and high mountains on the halfway mark (50 mile) of the steadily advancing Ledo Road. A small hospital there would provide a choice for the ambulances making the treacherous and dangerous trips from the combat zone to the hospitals at Ledo and save lives.

In pursuing this possibility and checking our assets, we found them to be:

1. Captain Irving Beck — Internist, laboratory, and pathology.
2. Captain John Dziob — Surgery, fractures, anesthesia, and neurosurgery.
3. Captain Isadore Garber — Internist and radiologist.
4. Captain Edward Greuninger — Eye, ear, nose and throat.
5. Lieutenant Milton Korb — Neurology.
6. Captain William Leet — Internist and nutritionist.
7. Captain Frederick Webster — General Medicine and surgery.
8. Major Eric Stone — Commanding officer and genito-urinary.

Not having thought about it before, it came to us as a surprise how well the group could have covered the field of medicine. Leave it to Fate to do the choosing! At any rate, the hospital would be our answer to the "Pool," at Ledo. It was a long, long shot, we knew; but when your back is to the wall challenged by the prospect of being dispersed, ending up only the Lord knows where, one has no choice but "to go for it"; and go for it we did with a vengeance. "Those who dare, do; those who dare not, do not."⁴



The Group of 7 on a boat to the Irrawadi River. Front left to right: Edward Greuninger, Irving Beck, William Leet, John Dziob. Back left to right: Isadore Garber, a sergeant, unidentified.

And so, it came to pass. Even though the project was conceived by us and not by the Army, it was sold to the "Top Brass" at Ledo, Assam by Major Stone. From then on, however, we saw to its construction and expansion, and successfully ran it and maintained it until we rejoined the 48th Evacuation Hospital on March 29, 1944 on the latter's return from Ramgahr in preparation for the "big push" by General Stillwell and the Merrill's Marauders.

We had been away from the 48th Evacuation Hospital for eleven months; and now the Discards had not only come back from the mission intact but had on their own initiative established and successfully maintained a hospital at Tincha to boot. Moreover, they were able to regain the parent outfit with a feeling of outstanding ac-



48th Evacuation Hospital reassembles. Left to right: John Dziob, unidentified, Irving Beck.

complishment — all over and above the call of duty.

The "Legion of Merit"? Some mention was made of it at our initial briefing at Ledo. We did not get it. Should we have? I leave that up to the reader. Now in looking back through the haze of forty-four years, and being none the worse for the experience, I can say that it was almost fun. But I have one regret, that those of my departed comrades are not here to relive through the magic of the pen those tumultuous days.

Acknowledgment

Many thanks to Doctor Irving Beck, who joined me at lunch on several occasions at the University Club, where we relived those times, jogged our memories, and compared his letters home with my diary as to the events depicted in the above paper. For further adventures of the Group of 7 consult the *Rhode Island Medical Journal*: "Ten Years Before Mash," Vol 65, No 12, Dec 1982. The Group of 7: Seven ordinary guys who together did an extraordinary job. By being "Johnny on the spot" we saved lives, controlled suffering and assuaged anxiety.

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PATIENT INITIALS (Optional) A.D.R.	AGE: years 54	SEX <input checked="" type="checkbox"/> MALE <input type="checkbox"/> FEMALE	DATE OF REACTION ONSET 12 Oct. 1986
DESCRIBE REACTION(S) Give signs, symptoms, diagnoses, course and relationship		CHECK ALL APPROPRIATE TO REACTION <input type="checkbox"/> DIED <input checked="" type="checkbox"/> TREATED WITH Rx DRUG <input checked="" type="checkbox"/> INPATIENT HOSPITALIZATION <input type="checkbox"/> SEVERE OR PERMANENT DISABILITY <input type="checkbox"/> EMERGENCY ROOM TREATMENT <input type="checkbox"/> TREATMENT IN PHYSICIAN OFFICE <input type="checkbox"/> NONE OF THE ABOVE	
SUSPECTED DRUG(S) (Trade Name is preferred. If a generic product, give manufacturer's name, lot number, and expiration date.) HYPERTENSION			
REASON FOR USE OF DRUG(S) HYPERTENSION	ROUTE P.O.	TOTAL DAILY DOSE 100mg.	DATES OF ADMINISTRATION 9 Sept.- 12 Oct. '86
OTHER DRUGS TAKEN CONCOMITANTLY (Exclude those used to treat reaction) None			
OTHER RELEVANT HISTORY (e.g., Concomitant Diagnoses, Pregnancy, etc.) None			
PHYSICIAN NAME AND TELEPHONE NUMBER J. Doe, M.D. 277-2550			
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Crohn's Disease in Ireland: Then and Now

Colles Anticipated Crohn et al by a Century

J. F. Fielding, BSc, MD, FRCPI, FRCP, FACG

Crohn's disease has been known in Ireland for over 150 years. In 1830 Abraham Colles, of Colles's fracture fame, wrote a paper on "Practical observations upon certain diseases of the anus and rectum."¹ One condition he elaborated on was organic stricture of the rectum. In this section he stated: "The disease spares neither sex nor rank; it most frequently attacks those who are about the meridian of life; sometimes, however, it afflicts children as early as the seventh or eighth year of their age." He also remarked: "In some cases a fistulous opening forms in the nates or perineum, which will admit a probe to pass into the rectum . . ." and "In some cases, especially in females, I have known the number of these fistulous openings to amount to twelve or twenty."

Later on in the course of the disease; ". . . it too frequently happens in females, that communication is formed between the rectum and the vagina, which causes the greater part of the faeces to pass through the latter. In men, but more rarely, a similar communication is established between the rectum and bladder."

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Based on a lecture given before the Division of Gastroenterology in the Department of Medicine, Rhode Island Hospital, Providence, Rhode Island, Thursday, October 20, 1987. Doctor Fielding was Chief Pro Tem, Gastrointestinal Division, Rhode Island Hospital.

He also commented on perianal disease: ". . . we often observe at the orifice of the anus the following appearance, which is indeed almost always present when the disease is seated near the external sphincter, namely, at each side of the anus a small projection, which on its external surface appears as a mere elongation and thickening of the skin, but internally presents a moist surface, not exactly like the lining membrane of the gut, nor yet can we say that it is ulcerated. These two projections lie close together below and diverge above, presenting a resemblance to the mouth of an ewer."

With regard to post mortem findings, Colles remarked: "All coats of the intestine were very much thickened except the peritoneal tunic, which when closely inspected is found to retain its healthy structure and appearance; the muscular, cellular, and mucous coats are thickened; the latter is moreover hardened and raised into the irregular ridges, or folds, but without ulceration."

I have no doubt that some of the patients Colles described would today be accepted as suffering from Crohn's disease. In 1846 and again in 1853² Dominic J. Corrigan, of aortic incompetence fame, reported a patient with diarrhoea in whom the wall of the ileum was much thickened and its mucosa had "Snail Track" ulceration. Walker and Fielding on reviewing the literature of the latter half of the last century found evidence for 29 patients presenting to Dublin Teaching Hospitals during that period of time who would today be classed as suffering from Crohn's disease.³ They applied strict criteria, and excluded a further seventeen possible cases. Of their 29 cases, 19 were male. Their ages (of the twenty-three patients whose ages were stated) ranged from 16

to 68 (average 31.6) years; 74 per cent were under the age of 40. Eight had macroscopic disease affecting the large bowel alone, 14 had combined large and small bowel disease, and six small bowel disease alone. The following features of Crohn's disease were mentioned in these case reports; enlarged mesenteric glands, entero-vesical fistula, intra-abdominal abscess, perforation, toxic dilatation, fatty degeneration of the liver, liver abscess, perianal disease, entero-cutaneous fistula, entero-enteral fistula, and successful operative bypass and resection procedures.

In addition to these case reports Redmond in 1891 described "A case of acromegaly."⁴ From looking at the plates in the article, the young girl almost certainly had hypertrophic osteoarthropathy, and, as she also had diarrhoea, it is possible that she was a further example of Crohn's disease seen in Ireland in the last century.

Thus, Crohn's disease existed in Ireland, as it did in London⁵ in the last century and it is not, as has been suggested,⁶ a "new" disease of this century.

I now wish to jump some seventy to eighty years and describe Crohn's disease as it exists in Ireland today, as seen through the eyes of one having a personal series of 72 patients referred from 64 different sources over a 10 year-period.⁷ Of the 72 patients, 37 were female. The age at diagnosis ranged from 12 to 72 (average 30.5) years. The duration of symptoms ranged from 1 to 444 (average 35.7) months. Whereas three-fifths of patients had their disease diagnosed within two years of the onset of symptoms, one patient in six had symptoms in excess of five years prior to diagnosis. The reasons for "delayed" diagnosis varied with disease site. Those with large bowel disease had previously been labeled as suffering from ulcerative colitis; or co-existent large-bowel Crohn's disease had been overlooked in patients presenting with perianal disease. Some patients with small-bowel disease had been thought to be suffering from intestinal tuberculosis, or labeled as "functional." Thirty-two per cent of the patients had small bowel disease, 26 per cent small- and large-bowel disease, and 42 per cent large-bowel disease. At some point 39.1 per cent had finger clubbing. Two-thirds of the patients had perianal disease, but it was symptomatic in only one patient in nine. Bowel was palpable in over half the patients but there was no correlation between the site of palpable bowel and the site of macroscopic disease. Skin and eye lesions occurred in one patient in four, and joint lesions in one patient in five. Er-

ythema nodosum was the commonest skin lesion; psoriasis was also significantly associated. Iritis was the commonest eye lesion, and arthralgia the commonest joint lesion. One patient had sclerosing cholangitis.

The crude risk of Crohn's disease amongst the parents and siblings of patients was 8.5 per cent.⁸ The relative risk compared with the general population was increased some twenty-five fold for siblings and fifty-fold for patients. The relative risk of ulcerative colitis was probably a quarter that of Crohn's disease.

The mean duration of follow-up was 5.84 years.⁹ The crude operative rate was 38.9 per cent, and the crude operative recurrence 32.1 per cent. The risk of surgery per patient per year was 13.91 per cent. The cumulative risk of surgery at nine years was 60 per cent, and the cumulative risk of further surgery was 66.8 per cent at 9 years. There was no operative mortality. Mortality was virtually double that expected¹⁰; this increase related to those diagnosed before their fortieth birthday.

Thus it can be seen that Irish patients with Crohn's disease fare similarly to their American fellow sufferers. A few points seem worthy of note: The mean duration of symptoms pre-diagnosis has fallen only from four to three years over the past fifty years. Large-bowel disease is on the increase, whilst perianal disease, which occurs more frequently with large-bowel disease, is on the decrease. Indeed, severe perianal disease is rarely seen today. Finally excess mortality has altered little over the years.

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PRECAUTIONS: General. Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (e.g., elderly, chronic alcoholics, patients on anticonvulsants, with malabsorption syndrome, or in malnutrition states) and severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur, frequently dose-related.

Use in the Elderly. May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, e.g., impaired kidney and/or liver function, concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see **WARNINGS** and **ADVERSE REACTIONS**) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly. In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura reported. Make appropriate dosage adjustments for patients with impaired kidney function (see **DOSAGE AND ADMINISTRATION**).

Use in the Treatment of Pneumocystis Carinii Pneumonitis in Patients with Acquired Immunodeficiency Syndrome (AIDS). Because of unique immune dysfunction, AIDS patients may not tolerate or respond to Bactrim in same manner as non-AIDS patients. Incidence of side effects, particularly rash, fever, leukopenia, with Bactrim in AIDS patients treated for *Pneumocystis carinii* pneumonitis reported to be greatly increased compared with incidence normally associated with Bactrim in non-AIDS patients.

Information for Patients. Instruct patients to maintain adequate fluid intake to prevent crystalluria and stone formation.

Laboratory Tests. Perform complete blood counts frequently. If a significant reduction in the count of any formed blood element is noted, discontinue Bactrim. Perform urinalyses with careful microscopic examination and renal function tests during therapy, particularly for patients with impaired renal function.

Drug Interactions. In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. Keep this in mind when Bactrim is given to patients already on anticoagulant therapy and reassess coagulation time. Bactrim may inhibit the hepatic metabolism of phenytoin. Given at a common clinical dosage, it increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When giving these drugs concurrently, be alert for possible excessive phenytoin effect. Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

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Carcinogenesis, Mutagenesis, Impairment of Fertility. Carcinogenesis. Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim. Mutagenesis. Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination; concentrations used exceeded blood levels of these compounds following therapy with Bactrim. Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities. Impairment of Fertility. No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

Pregnancy Teratogenic Effects. Pregnancy Category C. Trimethoprim and sulfamethoxazole may interfere with folic acid metabolism; use during pregnancy only if potential benefit justifies potential risk to fetus. Nonteratogenic Effects. See **CONTRAINDICATIONS** section.

Nursing Mothers. See **CONTRAINDICATIONS** section.

Pediatric Use. Not recommended for infants under two months (see **INDICATIONS** and **CONTRAINDICATIONS** sections).

ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION).** Hematologic. Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia. Allergic Reactions. Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schönlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. Periorbital nodosa and systemic lupus erythematosus have been reported. Gastrointestinal. Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia. Gastrointestinal. Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria. Neurologic. Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. Psychiatric. Hallucinations, depression, apathy, nervousness. Endocrine. Sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents; cross-sensitivity may exist. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Musculoskeletal. Arthralgia, myalgia. Miscellaneous. Weakness, fatigue, insomnia.

DOSAGE AND ADMINISTRATION. Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN. Usual adult dosage for urinary tract infections is one DS tablet, two tablets or four teaspoons (20 ml) *b.i.d.* for 10 to 14 days. Use identical daily dosage for 5 days for shigellosis. Recommended dosage for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses every 12 hours for 10 days. Use identical daily dosage for 5 days for shigellosis. Renal Impaired. Creatinine clearance above 30 ml/min, give usual dosage, 15-30 ml/min, give one-half the usual regimen, below 15 ml/min, use not recommended.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS. Usual adult dosage is one DS tablet, two tablets or four teaspoons (20 ml) *b.i.d.* for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS. Recommended dosage is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

HOW SUPPLIED: DS (double strength) Tablets (160 mg trimethoprim and 800 mg sulfamethoxazole)—bottles of 100, 250 and 500, Tel-E-Dose® packages of 100; Prescription Paks of 20 Tablets (80 mg trimethoprim and 400 mg sulfamethoxazole)—bottles of 100 and 500, Tel-E-Dose® packages of 100; Prescription Paks of 40 Pediatric Suspension (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 100 ml and 16 oz (1 pint); Suspension (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 16 oz (1 pint).

STORE TABLETS AT 15°-30°C (59°-86°F) IN A DRY PLACE PROTECTED FROM LIGHT. STORE SUSPENSIONS AT 15°-30°C (59°-86°F) PROTECTED FROM LIGHT.

P 1 0586



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YOCON® YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in *Rauwolfia Serpentina* (L.) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the CNS and produces a complex pattern of responses in lower doses than required to produce peripheral α-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Illustrations: Authors are urged to use the services of professional illustrators and photographers. Drawings and charts should always be done in black ink on white paper. Clear, black and white glossy photographs should be submitted, and such illustrations numbered consecutively and their positions indicated in text. Original magnifications should be noted. Illustrations defaced by handwriting or excessive handling will not be accepted. The figure number, indication of the top, and the name of the author must be attached to the back of each illustration. Legends for illustrations should be typewritten in a single list, with the numbers corresponding to those on photographs and drawings. Recognizable photographs of patients are to be masked and must carry with them written permission for publication.

Special arrangements must be made with the editors for excessive illustrations. Color plates are not acceptable.

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INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFervescent POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis

2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation

WARNINGS: **Hyperkalemia**—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute acidosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics, see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS, and OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics

2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.

3. Correction of acidosis, if present, with intravenous sodium bicarbonate

4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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TAKE CARE OF YOURSELF Rhode Island Department of Health



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If you know a physician who can benefit from peer education in a particular area of medical practice, please write Dr. William Colaiace, Chairman, Peer Review Committee on Physician Competency, Rhode Island Medical Society, 106 Francis Street, Providence, RI 02906. For more information, call the Society at (401)331-3207. All referrals are held in strict confidence.

HAVE YOU HEARD?

Congenital dislocation of the hip (CDH) can now be detected in infants through an electronic sensor developed by researchers at Queens University in Belfast, Northern Ireland. The computerized device is an improvement on the previous method in which a doctor checks for a "clunk" in the hip joint while manipulating the infant's limbs. Signals from four transducers, taped to the legs and hips, are fed to a microcomputer where they are analyzed and displayed on a screen in a graphic similar to an electrocardiogram. Diagnosis using the older technique often occurs too late for easy treatment. Through early diagnosis, a simple cure involves putting the baby in a plastic splint for three months. The new infant hip screener now offers a minimum accuracy rate of 86 per cent.

• • •

A new drug that is effective against the devastating disease known as "river blindness," or onchocerciasis, will be made available free of charge by its discoverer, a US based health products company. An estimated 19 million people are affected by the parasitic disease which threatens an estimated 85 million more in many third world countries. The infected individuals, usually coming from extremely poor and remote areas, suffer from many ailments including eye lesions that eventually lead to blindness. The drug, which doesn't restore sight to those already blinded by the disease, will prevent the disease from reaching that stage by killing the parasitic worm's larva and blocking worm reproduction. Donation of the drug, considered the best strategy to control the disease, will be coordinated by the company with the World Health Organization.

• • •

A new zipper technique to help in draining necrotic or infected tissue in patients with severe

abdominal sepsis is being used by J. L. Garcia-Sabrido, MD, PhD, of the Hospital Provincial, Madrid, and colleagues. According to a report in February's *Archives of Surgery*, a nylon/polyethylene zipper or zipper/mesh combination can provide easy abdominal access until treatment of the infected tissue is complete. Since 1982, 49 patients with necrotic pancreatitis and 15 patients with severe intra-abdominal sepsis due to intestinal perforations were treated. Mortality in both groups was sharply lower than expected, attributed to the open-abdomen zipper technique.

• • •

A limb-sparing treatment for patients with high grade, surgically removable skeletal and soft tissue sarcomas is being used at the University of Southern California's Norris Cancer Hospital in Los Angeles by its Bone and Soft Tissue Consultative Study Group, this from a recent *Oncology Times* issue. Prior to surgery, chemotherapy — most commonly cisplatin — is administered intra-arterially rather than intravenously, resulting in a higher concentration of the drug at the tumor site. Raymond A. Kempf, MD, says that on average, 50 to 90 per cent of the tumors are destroyed. Surgery follows the preoperative chemotherapy, and the section of the bone or soft tissue where the tumor is located is removed. In bone tumors, a steel prosthesis is implanted in place of the resected bone. Following surgery, patients are given supplemental chemotherapy to kill any metastases. The total treatment program consists of four cycles of preoperative chemotherapy at two-week intervals, followed by surgery, after which a year of postoperative chemotherapy, and sometimes radiation therapy, is initiated. Candidates for the program must be under 70 years of age and must not have previously undergone chemotherapy or radiation therapy.

PERIPATETICS

CARAFATE[®]

(sucralfate)

BRIEF SUMMARY

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate.

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that the simultaneous administration of CARAFATE with tetracycline, phenytoin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. The clinical significance of these animal studies is yet to be defined.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of drug-related tumorigenicity was found in chronic oral toxicity studies of 24 months' duration conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies have not been conducted.

Pregnancy: Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients, adverse effects were reported in 121 (4.7%). Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED

CARAFATE (sucralfate) 1-gm pink tablets are supplied in bottles of 100 and in Unit Dose Identification Paks of 100. The tablets are embossed with MARION/1712.
Issued 3/84

References:

1. Grossman MI: *Scand J Gastroenterol* 58 (suppl 15):7-16, 1980.
2. Marks IN, in Hellermans J, Vantrappen G (eds): *Gastrointestinal Tract Disorders in the Elderly*. Edinburgh, Churchill Livingstone, 70-81, 1984.
3. Krentz K, Jablonowski H, in Hellermans J, Vantrappen G (eds): *Gastrointestinal Tract Disorders in the Elderly*. Edinburgh, Churchill Livingstone, 62-69, 1984.



1595H7

The first International Child Health Foundation symposium held at the National Academy of Sciences featured **Dr Charles Carpenter**, physician-in-chief at The Miriam Hospital and professor of medicine, as one of several speakers. **Dr Carpenter** was selected to speak as an internationally recognized physician in diarrheal diseases.

• • •

The Radiological Society of North America recently presented the Cum Laude Scientific Exhibit Award to **Dr Kevin J. McEnery**, a resident in radiation medicine at Rhode Island Hospital.

• • •

Dr Barry L. Levin, a neurologist in Pawtucket, was named to the 15-member council of professional advisory committee chairmen and directors of chapter-affiliated clinics by the National Multiple Sclerosis Society.

• • •

A surgical oncologist, **Dr Harold J. Wanebo**, has been named chief of surgery at Roger Williams General Hospital and chief of the division of surgical oncology for Brown University School of Medicine.

• • •

Kent County Memorial Hospital has appointed **Dr Robert E. Baute**, a Warwick physician practicing internal medicine since 1970, as medical director.

• • •

Dr Charles Kuhn, III, responsible for the academic research activities of Pawtucket Memorial Hospital's Pathology Department, has been named Chief of Anatomical Pathology. His other responsibilities include surgical, autopsy and cytology pathology, as well as the Brown University Pathology Residency Department.

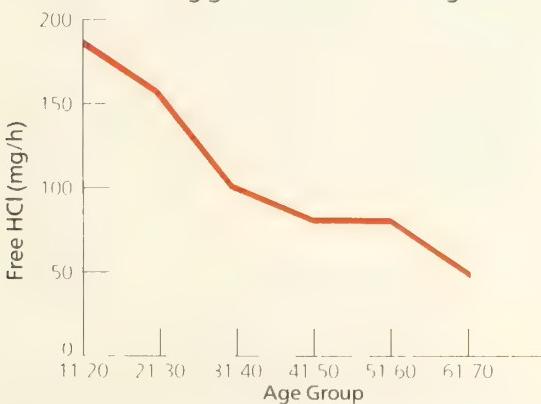
Specialized ulcer therapy

When advancing age signals reduced acid secretion



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Please see adjoining page for references and brief summary of prescribing information

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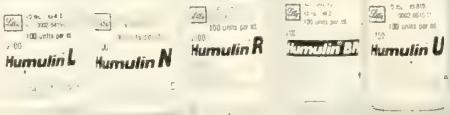
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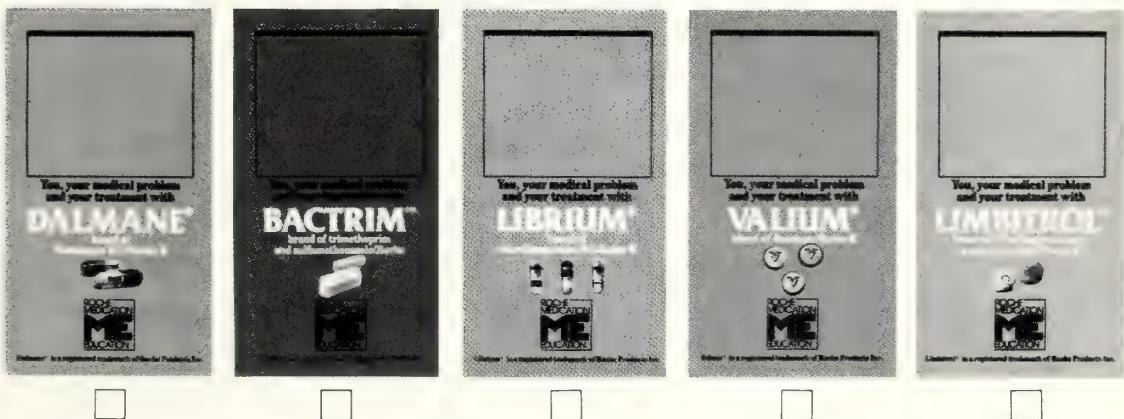
An ongoing Roche commitment to patient education

Roche has always believed that knowledge is each individual's key to good health and has long been committed to providing health care information to both professionals and the public. However, we have also always believed that the health care professional is and should be the prime source of medication information to patients. The Roche Medication Education (ME) program, begun in 1978, is one example of this commitment.

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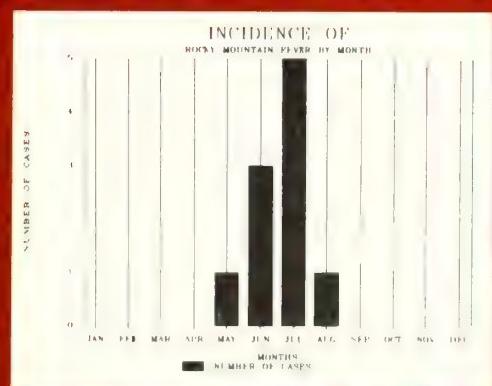
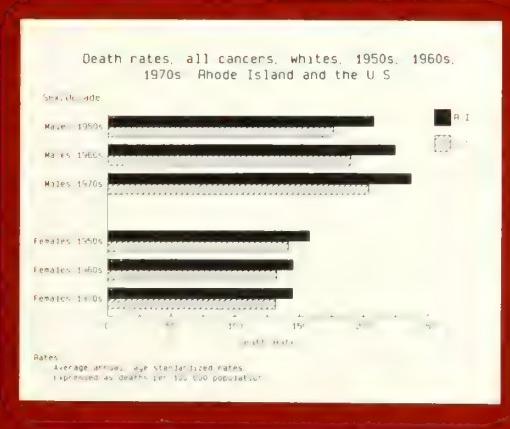


April 1988

Volume 71, Number 4

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Azorean (Machado-Joseph) Disease

EPIDEMIOLOGICAL PERSPECTIVES
IN RHODE ISLAND

Thalidomide and D.E.S. (They could happen again.)

Sometimes even the most promising drug may have unexpectedly adverse reactions in patients. Pre-market testing identifies most toxic drugs before release for patient-care use, but not all. Toxicity in some drugs can only be determined through adverse reactions detected among a larger number of patients over a longer period of time.

The plain truth is that a patient's health may be at risk. Adverse drug reactions cause death in approximately 30,000 patients annually in the United States alone. So, if you suspect an adverse drug reaction, please report it promptly. We may all live longer because you did.



The Adverse Drug Reaction Reporting Project

of the Rhode Island Department of Health

To report an ADR by phone, call **456-ADRS** weekdays between 9 and 5. To receive mailing forms and additional information, call the Health Department at 277-2901.

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In a recent survey, 4,120 participating physicians gave us their views¹ on INDERAL LA in the treatment of hypertension, angina and migraine.

INDERAL LA is their preferred beta blocker

...of the nearly three out of four physicians responding to the questionnaire, an impressive 97% rated INDERAL LA good to excellent for overall performance. Virtually all cited efficacy, tolerability, long-term cardiovascular protection and once-daily convenience as important factors in their choosing to prescribe INDERAL LA.

INDERAL LA promotes patient compliance

...Virtually every responding physician rated patient satisfaction with INDERAL LA to be as good as, or better than, other beta blockers.

Like conventional INDERAL Tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree and bronchial asthma.

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Please see next page for brief summary of prescribing information.

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60, 80, 120, 160 mg

The one you know best keeps looking better

60 mg 80 mg 120 mg 160 mg

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® LA brand of propranolol hydrochloride (Long Acting Capsules)

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. Inderal is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by Inderal, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Inderal LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with Inderal LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of Inderal Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

Inderal LA should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to Inderal LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, Inderal LA has been therapeutically equivalent to the same mg dose of conventional Inderal as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. Inderal LA can provide effective beta blockade for a 24-hour period.

INDICATIONS AND USAGE. **Hypertension:** Inderal LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. Inderal LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: Inderal LA is indicated for the long-term management of patients with angina pectoris.

Migraine: Inderal LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: Inderal LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. Inderal LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. Inderal is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with Inderal.

WARNINGS. **CARDIAC FAILURE:** Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitized and/or treated with diuretics, and the response observed closely, or Inderal should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of Inderal therapy. Therefore, when discontinuance of Inderal is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If Inderal therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute Inderal therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Inderal should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Inderal (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta blockers should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid function tests, increasing T₄ and decreasing T₃.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Propranolol should be used with caution in patients with impaired hepatic or renal function. Inderal (propranolol HCl) is not indicated for the treatment of hypertension emergencies.

Beta-adrenoceptor blockade can cause reduction of intraocular pressure. Patients should be told that Inderal may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if Inderal (propranolol HCl) is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncope, attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbital, and rifampin accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and lidocaine have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T₃ concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorogenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

PREGNANCY: Pregnancy Category C. Inderal has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. Inderal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: Inderal is excreted in human milk. Caution should be exercised when Inderal is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly blurred sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: Bronchospasm.

Ematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasisiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctiva reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. Inderal LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from Inderal Tablets to Inderal LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. Inderal LA should not be considered a simple mg-for-mg substitute for Inderal. Inderal LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION — Dosage must be individualized. The usual initial dosage is 80 mg Inderal LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS — Dosage must be individualized. Starting with 80 mg Inderal LA once daily, dosage should be gradually increased at three- to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE — Dosage must be individualized. The initial oral dose is 80 mg Inderal LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, Inderal LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS — 80-160 mg Inderal LA once daily.

PEDIATRIC DOSAGE — At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Reference:

- 1. Data on file, Ayerst Laboratories.

D7295/188



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DAW

'DYAZIDE' AS WRITTEN

Not for initial therapy. See brief summary.

without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B, corticosteroids or corticotropin/ACTH). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency.

Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions.

Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported.

Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine.

Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components.

Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The

following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (if hypokalemia), decreasing alkaline reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics); Necrotizing vasculitis, paresthesias, clonus, pancreatitis, xanthopsia and respiratory distress including oneonitis and pulmonary edema, transient blurred vision, saladenitis, and vertigo have occurred with the thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

BR5-DZ-145

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SK&F Co. 1987

Before prescribing, see complete
prescribing information in
SK&F Co. literature or PDR.
The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy directed to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hypokalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or



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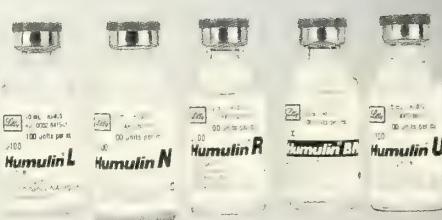


Any change of insulin should be made cautiously and only under medical supervision. Changes in refinement, purity, strength, brand (manufacturer), type (regular, NPH, Lente®, etc), species/source (beef, pork, beef-pork, or human), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.

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FISKE PRIZE COMPETITION

The Trustees of the Caleb Fiske Fund invite readers of the RHODE ISLAND MEDICAL JOURNAL to submit nominations for the 1988 Fiske Prize Competition for scholarly writing in medicine.

Readers may nominate either their own work or meritorious works by other authors.

Eligible for consideration are scientific articles, essays and books published anywhere, or submitted for publication, during the calendar year 1987. Original manuscripts that have not been submitted elsewhere are also eligible.

The 1988 competition is limited to medical topics but is not restricted to any particular clinical, socio-economic, or historical area of medicine or surgery.

Submissions must be in English.

Copies of written work for consideration should be submitted to the

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Cover: Graphs representing cancer deaths in RI/US from the RI Department of Health, and Rocky Mountain Spotted Fever occurrence in RI from Infectious Disease Division, The Memorial Hospital. Photograph of patient with Azorean (Machado-Joseph) Disease courtesy of Joseph H. Friedman, MD.

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EDITORIAL

Breast Health

The recent news about Nancy Reagan's breast cancer and its management have been distressing in many ways. It has reawakened the constant fear all women share about developing breast cancer and has perpetuated several misconceptions regarding the proper management of breast cancer.

It is important to recognize that Mrs. Reagan's cancer was detected only by use of a "routine" mammogram. There was no indication from her physical examination or medical history that she had breast cancer. The fact that she is a post-menopausal woman in the United States was reason enough for her to have an annual mammogram.

Her breast cancer was very small (7 mm or $\frac{1}{4}$ inch) and could have been detected only by the newer, more sensitive low-dose mammography machines. If this early breast cancer had not been detected by x-ray, it would have been another two to five years before it would have been large enough to feel, even in a thin woman such as Mrs. Reagan.

Despite the ability of routine mammography to detect breast cancer at a very early, more curable stage, only 10-15 per cent of all doctors order these x-rays for their patients at risk. The usual reasons given are the concern about exposure to too much radiation, patient discomfort and expense.

The new x-ray equipment exposes the breast to less radiation than the breasts receive in flying across the US or living in Denver for one week. The risk of developing a breast cancer from this exposure to radiation is less than one in a million.

Although the breasts are compressed during mammography to obtain the best possible pictures, the discomfort for most women is minimal, especially if they have the x-ray done after the menstrual period when the breasts are most tender.

The cost of a mammogram is not insignificant, but is covered by many health insurance plans. In order to make mammography available to all women, the Rhode Island Department of Health is coordinating a statewide reduced-fee screening mammography program. It is scheduled to begin with the next few weeks.

Increased numbers of mammograms have been done in recent years since the publicity about breast cancer generated by the experiences of Happy Rockefeller, Betty Ford, Shirley Temple Black, Betty Rollins, Rose Kushner, and others. These studies have resulted in the discovery of cancers at earlier stages than ever before.

When breast cancer first develops, it is confined to the mammary ducts. After an indeterminate period of time, the cancer breaks through the wall of the duct and infiltrates the underlying tissue. It is only after it begins to infiltrate that it is capable of spreading through the lymph channels or the blood to other parts of the body.

Mrs. Reagan is reported to have had a non-infiltrating intraductal cancer, a cancer in its earliest stages. These non-infiltrating cancers almost never spread to the lymph glands and are considered to be almost 100 per cent curable.

Radical mastectomy has saved many women's lives since it was first used in the 1880s. However, the disfigurement associated with this operation led to modifications in surgical technique and the development of alternative methods of management.

Modified radical mastectomy removes the entire breast and the lymph nodes and does not cause the deformity of radical mastectomy, which also removes the muscles from beneath the breast. Often the deformity can be minimized by an immediate reconstruction of the breast, usually by placing an expandable implant beneath the chest muscles. There is no evidence that immediate reconstruction compromises a woman's chance

for cure or makes it more difficult to detect recurrence in the future.

For the past 40 years many cancer centers around the world have been treating breast cancer effectively by removing the cancerous lump and giving radiation therapy to the breast and surrounding area over a period of several weeks. The results of this therapy, which allows the woman to keep her breast, appear to be equal to the results of either radical or modified radical mastectomy.

Although no treatment can cure all women of breast cancer, the cure rates or years of control appear to be the same for the same stages of breast cancer regardless of which of the above treatments is chosen. Removing more tissue probably does not increase the chances for cure or change the possibility of cancer recurring in the area of the breast.

Mastectomy or lumpectomy-radiation therapy treats only the local breast cancer. Several factors are taken into consideration to determine whether or not a woman with breast cancer will benefit from either chemotherapy or hormone therapy. When the diagnosis of breast cancer has been made, the patient is evaluated to determine whether or not there is any indication of spread, commonly to the lungs, liver, and bones.

Lymph glands are carefully examined for metastases after removal. The cancer itself can be analyzed to determine if it is sensitive to hormones. The presence or absence of estrogen and progesterone receptors on the cancer cells can assist in selecting the appropriate therapy for an individual patient. But this test can be done only if there is a certain minimum amount of cancer to be tested, usually a cancer that measures at least one centimeter across (10 millimeters). Mrs. Reagan's cancer was only seven millimeters across and probably could not be tested for these receptors.

The team of physicians involved in determining the proper treatment for a breast cancer patient takes into consideration the kind of cancer and its size; the status of the lymph nodes; the results of the tests of the lungs, liver, and bone; and the estrogen receptor test results. Systemic treatment with chemotherapy or hormones is recommended only to those who will benefit from the treatment.

In brief, if it can be determined that a breast cancer is small and presumably early in its development, a woman could participate in reaching the appropriate treatment decision. Since most small breast cancers cannot be diagnosed

on the day of the biopsy, the patient would have time before any further surgery is performed to seek other opinions, read appropriate pamphlets and books, and discuss her treatment options with her family.

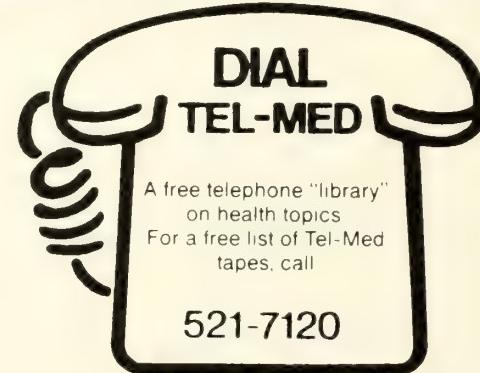
Even if the diagnosis of cancer is made on the day of biopsy, the patient can still safely take the time to make her decision. This decision must be made as calmly as possible and cannot be made while under the stress of hearing that the biopsy demonstrated cancer. There is no change in the long-term outcome of treatment if there is a delay of a few weeks between biopsy and further surgical treatment.

The requirements for lumpectomy and radiation therapy are that the chances for cure not be diminished and that the breast after treatment not be deformed. Perhaps Mrs. Reagan agreed to mastectomy because it was thought that a lumpectomy for her would leave a deformed breast.

Although Mrs. Reagan seems to have had excellent medical care for her breast cancer and participated in the decision for mastectomy, many other women with breast cancer can now exercise their right to save their breasts without compromising their chances for a healthy future.

Arnold H. Herman, MD, FACS

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and United Way of Southeastern New England

EDITOR'S MAILBOX

Ginsburg and Oppenheimer Disease



To The Editor:

Thank you for sending me a copy of the *Journal* of November 1987 containing the Editorial titled "Poetic Justice." The fact that you got the story [of the first description of "Crohn's Disease"] right and remembered it all these years was most gratifying to me. Unfortunately, I am not as hale and hearty as I at times appear. I go into training for my public appearances. Actually, I am in retreat on all fronts. I am officially 90 years of age. I was really deeply affected by your exhibition of gentlemanliness.

Leon Ginsburg, MD

Doctor Ginsburg, and the late Gordon D. Oppenheimer, were the first to recognize the significance of regional enteritis (described in 1932). It later became known as Crohn's Disease because Crohn's name appeared first on the published report.



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Cancer in Rhode Island, an Old Urban State

Urbanization Need Not Condemn Rhode Island to Excessive Cancer Death Rates

John P. Fulton, PhD
Jay S. Buechner, PhD
Ruth S. Baker, MS
John T. Tierney, MSW
H. Denman Scott, MD

In developed Western nations urban areas have higher cancer death rates than non-urban areas, mainly from cancer of the lung, colon-rectum, bladder, and female breast, although other cancer sites are involved, as well. These urban/non-urban differences have decreased with time, but remain substantial. Research suggests that cancer death rates are higher in urban areas because urban dwellers have lifestyles and jobs which expose them to higher levels of carcinogens and lower levels of cancer-preventive nutrients.¹

Rhode Island is one of the most urbanized states in the United States (US). In 1980, 87 per cent of Rhode Island residents lived in urban places,

as defined by the Census Bureau. Only the populations of New Jersey, the District of Columbia, and California had higher proportions of urbanites (89.0, 100, and 91.3 per cent, respectively). In comparison, only 74 per cent of the US population were classified as urban dwellers in 1980.²

Urbanization is not new in Rhode Island. The state has been highly urbanized for more than a century. More than half (56 per cent) of the Rhode Island population lived in urban places in 1850. In 1880, when a mere 28 per cent of the total US population were classified as urban dwellers, 82 per cent of the Rhode Island population lived in urban places.³

Rhode Island also stands out among other states for the severity of its cancer burden. In the 1970s its average annual age-adjusted cancer death rate was the highest among the states for white males, fourth highest for white females.⁴

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We explored the hypothesis that *Rhode Island's level of urbanization may contribute to its high cancer death rates*, by looking for parallels between Rhode Island's cancer experience and the cancer experience of other urban areas in developed Western nations. From the literature on this subject, we formulated four questions to guide our study:

1. With age, sex, race, and geographic region controlled, are Rhode Island's cancer death rates closer to the rates of more-urban than less-urban states?

2. Has the Rhode Island/United States differential in cancer death rates decreased with time?

3. Does cancer mortality in Rhode Island exhibit an urban profile? (Compared to the experience of the United States as a whole, are Rhode Island's death rates higher for cancer of the respiratory system, digestive system, bladder, and female breast, and about equal for cancer of other sites?)

4. Does an urban/non-urban differential in cancer death rates exist within Rhode Island? Has this intrastate differential decreased with time? Does it exhibit an urban profile? (Compared to the experience of less-urban areas of Rhode Island, are the death rates of more-urban areas higher for cancer of the lung, colon-rectum, bladder, and female breast, and about equal for cancer of other major sites?)

We looked for answers to these questions using published cancer death rates for counties in the United States over three decades, 1950-1959, 1960-1969, and 1970-1979. We found that Rhode Island's cancer experience was very similar to the cancer experience of other urban places in developed Western nations, suggesting that Rhode Island's level of urbanization contributes to its high cancer death rates. We discuss the implications of these findings for cancer control work in Rhode Island.

Methods

Cancer death rates were obtained from the 1983 publication, *US Cancer Mortality Rates and Trends, 1950-1979*.⁵ Each average annual rate is specific for decade, geographic area, cancer site, sex, and race. Each was age-adjusted by applying age-specific cancer death rates (for five year age-groups 0-4 through 80-84 and 85+) to a standard population (the US population in 1970). Each rate is expressed as "deaths per 100,000 population per year." Rates are available for the US, each state (and the District of Columbia), and each county.

We limited our geographical comparisons of

rates to those which could be made from the published rates. For example, Rhode Island rates were compared with US rates, not with US rates exclusive of Rhode Island, because the latter were unavailable. Similarly, Washington County rates were compared with Rhode Island rates, not with Rhode Island rates exclusive of Washington County, because the latter were unavailable. This restriction may have slightly reduced the differences between sub-area rates and whole-area rates. Fortunately, to the extent that this reduction occurred, it had a "conservative" influence on our findings, making it more difficult to demonstrate differences between geographic areas, and thus to answer our study questions affirmatively.

We compared rates, using the difference of proportions test as a test of statistical significance. All differences of rates discussed in this paper are statistically significant at the $P<0.05$ level, using the two-sample test for binomial proportions (normal distribution; one-tailed test), unless otherwise specified.

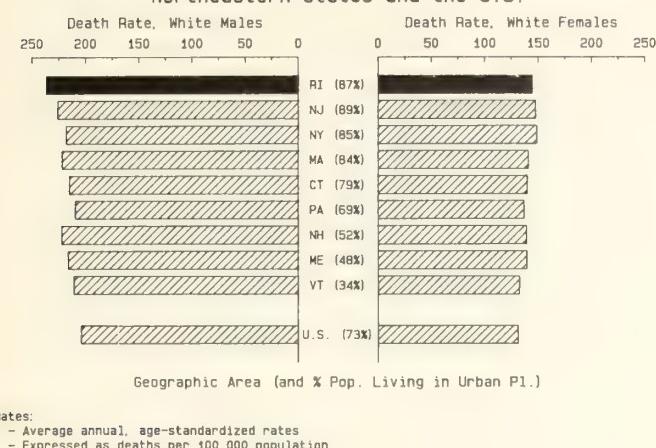
We limited our study to the cancer death rates of whites for two reasons. First, white and non-white cancer death rates differ in the US, and therefore should be disaggregated when comparing the cancer death rates of two or more areas having different proportions of white and non-white residents. Second, so few non-whites died of cancer in Rhode Island between 1950 and 1979 (979, or 33 per year), that the rate comparisons contemplated for our study would have been very difficult to interpret for non-whites. Any analysis of Rhode Island's non-white cancer death rates requires special attention to the problems inherent in the use of rates based on small numbers. We are undertaking a separate analysis of non-white cancer death rates in Rhode Island.

Throughout this paper, the term "urban" is used in accordance with the US Census Bureau's definition of urban places: "places of 2,500 or more inhabitants incorporated as cities, villages, boroughs . . . , and towns . . . [except rural portions of extended cities], . . . census designated places . . . of 2,500 or more inhabitants, and other territory, incorporated or unincorporated, included in urbanized areas."²

Results

Question 1. Rhode Island's cancer death rates were closer to the rates of more-urban than less-urban states as recently as the 1970s (with age, sex, race, and geographic region controlled). Figure 1

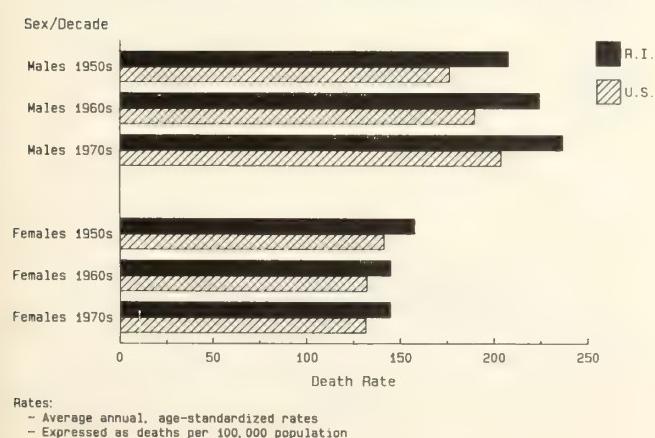
Figure 1
Death rates, all cancers, whites, 1970-1979:
northeastern states and the U.S.



demonstrates that Rhode Island's rates were more like the rates of the four other "more-urban" Northeastern states (NJ, NY, MA, CT) than the rates of the four "less-urban" Northeastern states (PA, NH, ME, VT) or the United States as a whole. The average male and female rates were higher in more-urban than less-urban states. Rhode Island's white male rate, 236.9, was highest of all the states. Rhode Island's white female rate, 144.9, was the median rate of the more-urban states.

Question 2. The Rhode Island/US differential in cancer death rates decreased slightly between 1950 and 1979 (Figure 2). In the 1950s, Rhode Island's white male rate (208.0) was 18 per cent higher than the US white male rate (176.6); in the 1970s it was 16 per cent higher than the US rate (RI: 236.9; US: 204.1). Rhode Island's white female rate was 11 per cent higher than the US rate in the 1950s (RI: 157.8; US: 141.6), and 10

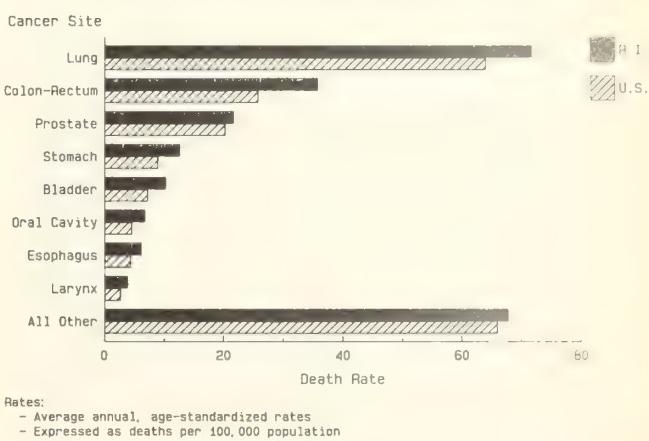
Figure 2
Death rates, all cancers, whites, 1950s, 1960s,
1970s: Rhode Island and the U.S.



per cent higher than the US rate in the 1970s (RI: 144.9; US: 131.7).

Question 3. Cancer mortality in Rhode Island exhibited an urban profile as recently as the 1970s. Compared to the experience of the United States, Rhode Island's white cancer death rates were higher for cancer of the respiratory system, digestive system, bladder, and female breast, and about equal for cancer of other sites. Rhode Island/US rate differentials were examined for each of 33 major anatomical sites and site groupings, and listed individually in Figures 3 and 4 if (a) the Rhode Island white rate exceeded the US white rate by at least one death per 100,000 population, and (b) the difference was statistically significant, as specified above. Other sites were aggregated and listed as "all other"; for these sites, Rhode Island rates were almost identical to US rates. For white males, differentials which met these criteria were found for respiratory sys-

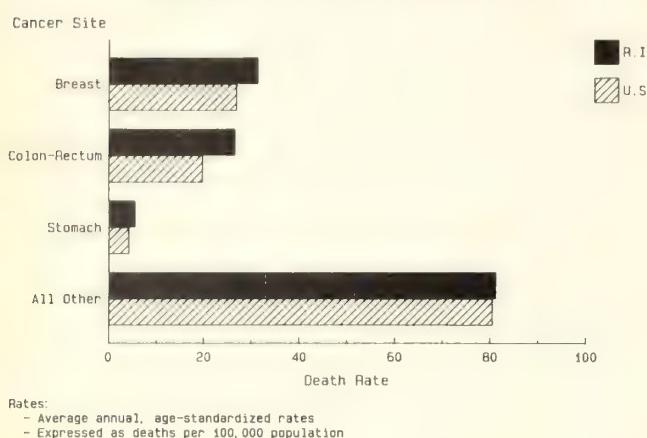
Figure 3
Death rates, selected cancers, white males,
1970-1979: Rhode Island and the U.S.



tem sites (lung and larynx), digestive system sites (colon-rectum, stomach, oral cavity, and esophagus), and bladder. A small differential was also found for cancer of the prostate (RI: 21.7; US: 20.3). For white females, differentials were found for digestive system sites (colon-rectum, stomach) and female breast.

Male cancer mortality in Rhode Island exhibited an urban profile as recently as the 1970s, even when compared with New Jersey, the most highly urbanized Northeastern state. Rhode Island/New Jersey white male rate differentials were examined for each of 33 major anatomical sites and site groupings. Sites were listed indi-

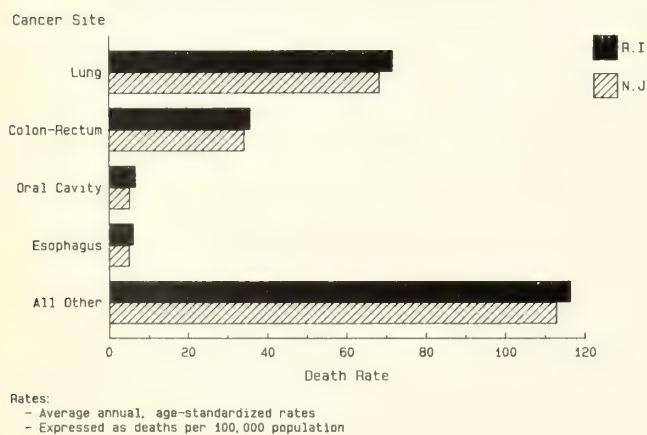
Figure 4
Death rates, selected cancers, white females,
1970-1979: Rhode Island and the U.S.



ividually in Figure 5 if they met both of two criteria: (a) the Rhode Island site-specific cancer death rate exceeded the New Jersey rate by at least one death per 100,000 population, and (b) the difference was statistically significant, as specified above. The sites which met these criteria included: lung (respiratory), and oral cavity, esophagus, and rectum (digestive). Other sites were aggregated and listed as "all other."

Question 4. An urban/non-urban differential in cancer death rates existed within Rhode Island throughout the 1950-1979 period. Washington County is the least urbanized county in Rhode Island, and has been for some time; the four other Rhode Island counties are considerably more urbanized. As late as 1980, only 47 per cent of Washington County residents lived in urban areas, as compared with 82 per cent of Newport County residents, 92 per cent of Providence County residents, 93 per cent of Kent County

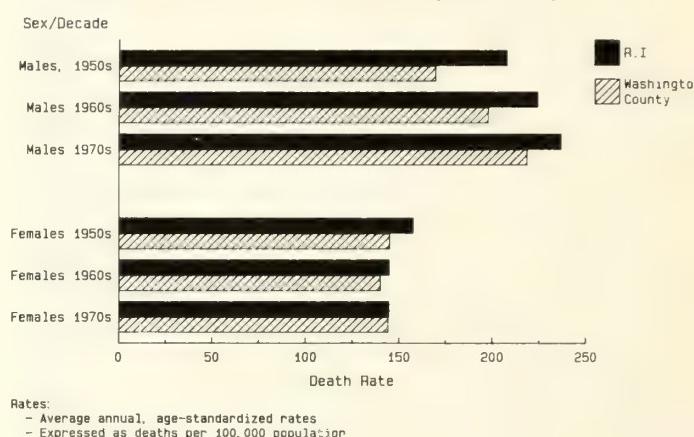
Figure 5
Death rates, selected cancers, white males,
1970-1979: Rhode Island and New Jersey



residents, and 97 per cent of Bristol County residents.² In 1950, a mere 28 per cent of Washington County residents lived in urban areas, as compared with 63 per cent of Newport County residents, 74 per cent of Bristol County residents, 86 per cent of Kent County residents, and 92 per cent of Providence County residents.⁶

As Figure 6 demonstrates, white cancer death rates for Rhode Island as a whole appear higher than white cancer death rates for Washington County in the 1950s (males and females), 1960s (males and females), and 1970s (males only). However, none of the female rate differentials were statistically significant, as specified above. The male intrastate differential decreased over time, from 18 per cent in the 1950s to eight per cent in the 1970s.

Figure 6
Death rates, all cancers, whites, 1950s, 1960s,
1970s: Rhode Island and Washington County, R.I.



As late as the 1970s, white male cancer mortality in more-urban areas of Rhode Island exhibited an urban profile. Compared to the experience of Washington County white males, the death rates of all Rhode Island white males were higher for cancer of the colon-rectum, oral cavity, and larynx. Other differences were not statistically significant (Figure 7).

Discussion

Considerable evidence supports the hypothesis that Rhode Island's level of urbanization may contribute to its high cancer death rates:

- In the 1970s, Rhode Island's white cancer death rates were similar to those of other more-urban Northeastern states, higher than those of less-urban Northeastern states. Taken as a whole, the Northeast, which is far more urbanized than the rest of the United States, and has been so

since at least 1790,⁷ had higher cancer death rates than the rest of the nation in the 1970s.

- The Rhode Island/US differentials in white cancer death rates decreased slightly between 1950 and 1979.

- Compared with the United States as a whole, white cancer mortality in Rhode Island exhibited an urban profile as recently as the 1970s. Cancer death rates were higher in Rhode Island for respiratory system sites, digestive system sites, bladder, and female breast. Even when compared with highly urban New Jersey in the 1970s, white male cancer mortality in Rhode Island exhibited an urban profile.

- An urban/non-urban differential is observable within Rhode Island for white males; it decreased between 1950 and 1979, and exhibited an urban profile as recently as the 1970s.

That Rhode Island has an urban cancer profile should not be surprising. Of all the states, Rhode Island is a prototypical urban state. Founded upon marginally fertile soil, Rhode Island agriculture began yielding its labor supply to industry before 1800. Rhode Island's first textile mill was built in the 1790s. Others followed so quickly that mill owners looked to Europe and Canada to supplement the State's native labor. Towns were built to house laborers close to their work, thus concentrating the growing population. No wonder, then, that more than 50 per cent of the population lived in urban places by 1850, more than 80 per cent by 1880, and more than 90 per cent by 1910.³

Causes Implicated in Urban/Non-Urban Differentials

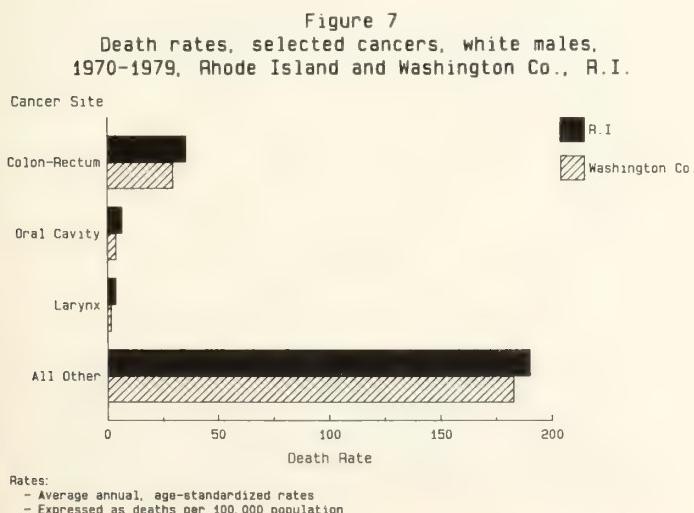
The typical urban cancer profile in the Western world has been attributed hypothetically to ur-

ban lifestyle, occupational exposures, and general environmental exposures, in that order of importance. Historically, urbanites have consumed more tobacco and alcohol than their non-urban counterparts. Both substances are important causes of upper digestive system cancers, and tobacco is the major cause of respiratory cancers. Urbanites have also consumed more fat and less fiber than others. Although the links between diet and cancer are not fully elaborated, there are data which suggest that diets high in fat and low in fiber either promote cancer of the colon-rectum or do not protect the colon-rectum from the effects of other cancer-causing agents. Occupational exposures to carcinogens tend to be concentrated in industrial urban settings, although it is now believed that less than five per cent of cancers arise from these causes. Environmental exposures (air and water pollution) are also believed to play a minor role in producing urban/non-urban differentials in cancer death rates.¹

Undoubtedly, tobacco use should be suspected as an important cause of Rhode Island's urban cancer profile. Tobacco use is known to cause cancer of the lung, mouth, pharynx, larynx, esophagus, bladder, and pancreas, as well as other minor sites. For males, Doll and Peto⁸ estimate that tobacco use causes 91 per cent of lung cancer; 75 per cent of mouth, pharynx, larynx, and esophageal cancer; 56 per cent of bladder cancer; and 40 per cent of pancreatic cancer. For females, they estimate that tobacco use causes 77 per cent of lung cancer; 43 per cent of mouth, pharynx, larynx, and esophageal cancer, 29 per cent of bladder cancer; and 25 per cent of pancreatic cancer.

In the 1970s, the Rhode Island cancer death rate for white males exceeded the US cancer death rate for white males by 32.8/100,000. Cancers of the lung, bladder, oral cavity, esophagus, and larynx, all attributable in part to tobacco use, accounted for 15.9/100,000 of this excess, or 48 per cent.

Around 1975, a greater proportion of adults in Rhode Island than in the US as a whole smoked cigarettes. The prevalence of cigarette smoking was measured in Rhode Island in 1975, and in the US in 1976. At that time 44.2 per cent of adult males (ages 20+) in Rhode Island smoked, versus 41.9 per cent of adult males in the US; 36.8 per cent of adult females in Rhode Island smoked, versus 32.0 per cent of adult females in the US.^{9, 10} By 1985, the Rhode Island/US smoking differential had decreased to almost zero for



adult males, and to about two percentage points (seven per cent) for adult females. At that time about 33 per cent of adult males smoked cigarettes in both populations; about 30 per cent of adult Rhode Island women and about 28 per cent of adult US women smoked cigarettes.^{11, 12} Despite the decrease in the Rhode Island/US smoking differential, the effects of the former differential will be observed for some time, because of the considerable lag between onset and diagnosis of many types of cancer. Also, Rhode Island/US differentials may have existed for tobacco use other than cigarette smoking, for which only very recent data are available.

The urban diet, which tends to be high in fats, higher than non-urban areas in alcohol, and low in fiber, should also be suspected as a possible cause of Rhode Island's urban cancer profile. Cancer of the esophagus has been linked to high consumption of alcohol, especially in combination with smoking. Cancer of the stomach has been associated with diets lacking in fresh fruits and vegetables and high in foods which have been pickled, salted, or smoked. Cancers of the colon and rectum are more common in populations whose diet is high in fat and low in fiber. Cancer of the prostate and cancer of the female breast have been tenuously linked with fat consumption.¹³

Cancers of white males in Rhode Island which are strongly associated with diet (including alcohol consumption), ie, cancer of the esophagus, stomach, and colon-rectum, accounted for 15.5/100,000 deaths in excess of US cancer death rates in the 1970s, or 47 per cent of the total Rhode Island/US differential for white males (32.8/100,000). Cancers of white females in Rhode Island which are strongly associated with diet, ie, cancer of the stomach and colon-rectum, accounted for 8.1/100,000 deaths in excess of US cancer death rates in the 1970s, or 61 per cent of the total Rhode Island/US differential for white females (13.2/100,000).

Little information has been collected on the specific dietary practices of Rhode Islanders, because the cost of collecting such information is prohibitively high. Measuring the dietary practices of any population is extremely difficult. People find it very difficult to recall the foods they eat, even when questioned about meals eaten one day previously. Information about portion size, means of preparation, and nutrient content, eg, fat content, is notoriously unreliable, unless respondents or subjects keep detailed diaries, a costly process. Even when such diaries are kept,

information about important nutrients must be estimated. In short, the cost of usable information may be too high to justify its collection at a time when the links between diet and cancer, although strong, need further study. Nonetheless, given the present state of our knowledge, the Rhode Island diet must be suspected as a cause of elevated death rates for digestive system cancers.

Some known occupational causes of cancer may contribute to the differential in cancer death rates between Rhode Island and the US. For example, aromatic amines, which may have been used in Rhode Island's dyeing industries, are known causes of bladder cancer.¹³ Asbestos, to which Rhode Islanders in various trades may have been exposed, is a known cause of lung cancer.¹³ Lag times between exposure to these carcinogens and cancer deaths may be long. Therefore, part of the differential in cancer deaths between Rhode Island and the US in the 1970s may have been caused by differential occupational exposures in the 1940s, 1950s, and 1960s. In part because of these long lags, and in part because systematic measurement of occupational exposures to known carcinogens was not undertaken in the past, the extent to which occupational causes have contributed to excess cancer deaths in Rhode Island is largely unknown.

It is very difficult to estimate the contribution of general environmental exposures to excess cancer deaths in Rhode Island. Nonetheless, at least one potential environmental cause should be considered suspect: radon. Radon is a known cause of lung cancer, and has been found at high levels in at least some private residences in Rhode Island. Until proven otherwise, radon should be considered a possible, partial cause of Rhode Island's high lung cancer death rates. When a current survey of radon levels in a representative sample of Rhode Island residences is completed, we shall be able to assess the effect of this environmental exposure more fully.

Learning More with Surveillance and Special Studies

Although Rhode Island will continue to be one of the most urbanized states in the US, urbanization does not condemn our state to excessive cancer death rates. To free Rhode Islanders of this problem, we must understand the causes which elevate cancer death rates in urban places. This paper represents an outline of our understanding thus far. We are building on this understanding by collecting and analyzing comprehen-

hensive surveillance data to locate cancer, to measure it, and to monitor changes in its location and measurements.

As exemplified by the present analysis, it is important to locate concentrations of cancer demographically, spatially, and temporally. Cancer is not found uniformly in any of these dimensions. For example, cancer tends to be concentrated in particular demographic subgroups, defined by age, race, sex, and socioeconomic status. Mainly because these groups have different residence patterns, cancer may be concentrated in particular geographic areas as well. It is important to note this. Spatial concentrations of cancer are caused primarily by the demographic characteristics (and closely related behavioral characteristics) of residents, and secondarily, even rarely, by spatial concentrations of carcinogenic substances or processes. Demographic *changes* also cause cancer to be concentrated temporally. For example, migrants with distinct behaviors may move into or out of state, bringing or taking with them high or low rates of cancer. A population may age, experiencing higher rates of cancer.

Surveillance data may be used to measure cancer in a variety of ways, including incidence, stage (extent of spread) at diagnosis, and mortality. They may also be used to measure or estimate prevalence, disability, and rates of cure.

Changes in the locations and measurements of cancer are monitored closely because they may yield clues about the causes of cancer. Observable changes in cancer may help us to find observable changes in causes, but establishing links between the two is complicated, especially when long time lags exist between the onset of cancer and its diagnosis. To cope with such difficulties, a well-planned surveillance data set must be collected at regular intervals (sometimes continuously, as in the case of registry data) over a long period of time. Changes in the locations and measurements of cancer are also used to evaluate the effectiveness of cancer control programs. Evaluations which measure changes in cancer incidence must also cope with time lags between the onset of cancer and its diagnosis, and may have to run for more than a decade.

The Rhode Island Department of Health has been developing its cancer surveillance tools for many years. Death certificate information represents the oldest and most reliable tool for observing cancer trends in Rhode Island, as elsewhere. The Rhode Island Health Interview Survey was fielded in 1972, 1975, 1980, and 1985, yielding information on personal behaviors which

affect cancer incidence and cancer detection. Recently, the Rhode Island Cancer Registry was established as a third major cancer surveillance tool. With funds specifically appropriated for cancer registration and control by the Rhode Island General Assembly, and in collaboration with the Hospital Association of Rhode Island (HARI), the Registry collects data on all cases of cancer (primary tumors) diagnosed on or after October 1, 1986 in Rhode Island. This information will be used to measure the incidence of cancer in demographic subgroups of the Rhode Island population, in geographic subareas of the State, and over periods of time.

Sometimes, surveillance data alone reveal sufficient information on a particular problem to begin planning for its solution, but frequently additional information is required before planning should be contemplated. Special studies are designed for this purpose, usually to collect comprehensive information from a target population or geographical area narrowly defined by surveillance. Building on surveillance findings in this way, the cost-effectiveness of special studies can be maximized. For example, the Department of Health has implemented a special study to learn more about cancer of the cervix in Rhode Island. Surveillance information had revealed that about 20 Rhode Island women die of this disease each year. Deaths from cancer of the cervix are considered largely avoidable, given current technologies for screening and treatment.¹⁴ The Department will attempt to determine if such deaths can be prevented by improving the present screening system, using data from three sources: the medical charts of a sample of women who have been treated for invasive cancer of the cervix; telephone interviews of a sample of Rhode Island women ages 40 and above; and telephone interviews of a sample of Rhode Island physicians who provide primary care.

Planning Effective Interventions

Regular surveillance data, supplemented by in-depth data from special studies, provide one of the ingredients for successful cancer-control planning. However, other ingredients are just as essential. Successful planning requires the recruitment of those institutions and individuals in the community who have a stake in the outcome of the planning process, no small task in cancer control. Wide community representation is necessary to give priority to the many needs uncovered by planning data. No community has sufficient resources to address all of its cancer control

needs at once. Once priorities have been set, planning requires additional information to design successful interventions. Sometimes this information is available from the literature, sometimes not. Frequently, additional information is necessary which may only be obtained by evaluating a small pilot intervention in the community. Once this information is known, larger interventions may be designed. However, planning does not end with the fielding of community-wide interventions. As it begins to establish cancer control needs, planning continues, while evaluation of the success of interventions in meeting those needs and the designing of more successful or efficient interventions is pursued.

Conclusion

Urbanization does not condemn Rhode Island to excessive cancer death rates. Just as we have illustrated in this study, Rhode Island's overall cancer problem can be broken down into understandable pieces with the appropriate information. Building on this information with planning, followed by thoughtfully designed programs, we shall be prepared to address many of these pieces successfully.

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Azorean (Machado-Joseph) Disease

Rhode Island Physicians Alerted to Recognize Disorder in the Local Azorean Community

Joseph H. Friedman, MD

In 1972 two independent reports appeared describing kindreds from southeastern Massachusetts, primarily the Fall River area, with a familial neurologic disorder.^{1,2} The first report traced the family tree back to one individual, William Machado,¹ who lived in the town of Bretanha on the island of São Miguel in the Portuguese Azores. The second report concerned the Thomas family,² described only as being of Portuguese descent. Since these reports were published, other kindreds with this disorder have been described among Portuguese immigrants to this country, the Joseph family in northern California³ and an unnamed family in Massachusetts.⁴ Surveys in the Azores⁵⁻⁷ have identified the disease there as well as Portugal.⁸ Each reported kinship has been unrelated. Complicating understanding of the disorder, however, are reports of families without Portuguese ancestry who appear clinically to suffer from a similar disorder.^{9,10}

The Azores are a group of islands in the Atlantic Ocean off the coast of Portugal, settled predominantly by people from Portugal. The disease referred to in this paper and first described in the English literature in 1972 had long been known in the Azores as *doenca de tropeção* or "stumbling disease." Interestingly, while American physicians have traced the disorder to

the Azores, many Azoreans, believing that the disorder actually was a venereal disease, had concluded that the disorder was brought to the Azores from the United States by 19th century whalers and fishermen.¹¹ In the Azores the stumbling disease is considered a cause for shame due in part to folk beliefs which attribute the malady to incest or to a venereal disease, as well as to the embarrassment caused by the ataxic gait, which uninformed observers believe is due to drunkenness.

There are three general subtypes of this disease,^{12,13} with a large degree of overlap. In all cases there is autosomal dominant inheritance with complete penetrance. That is, 50 per cent of the offspring of an affected parent will develop the disorder. Most commonly the disease begins between the ages of 20 and 50 but may also occur in children. It begins with gait ataxia, a peculiar, lurching type of walking abnormality very much akin to that of a drunkard. Patients with more advanced disease may also develop limb clumsiness. Other features which are variably present in the different subtypes include: progressive external ophthalmoplegia, nystagmus, spasticity, Babinski reflexes, mild weakness, distal muscular wasting, parkinsonism, spastic dysarthria, dysphagia, fasciculations, and peripheral neuropathy. The intellect appears to be preserved in all cases. Bladder and bowel function usually remain intact (although they may appear to be affected due to the patient's inability to get to the toilet). Emotional incontinence may also occur.¹¹

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The three main types of Azorean disease have been classified on the basis of phenomenology since there are no currently known biochemical markers. The genetic abnormality is thought to be identical in the different variants. One subtype of the disease affects patients with mainly cerebellar abnormalities. Another is characterized by gait ataxia plus major involvement of pyramidal and extrapyramidal systems producing parkinsonism or dystonia and spasticity. The final subtype embraces patients who have gait ataxia with distal muscular atrophy. For no apparent reason various authors have different numbering systems despite using the same classification scheme.^{12, 13} In each of these types gait ataxia and some abnormality of eye movements occur.

Case Reports

Case 1. This 61-year-old woman was referred for gait abnormality. She began to develop gait problems in her forties followed by hand tremors. She initially responded to trihexiphenidyl. As the illness progressed she became unable to walk. Despite the occurrence of extraocular muscle dysfunction, she did not complain of diplopia until two years after her eyes became dysconjugate. Her major complaint was of severe dysesthesia in her hands and feet. There was no history to suggest dementia or incontinence. Her history was positive for a lineal descent from the Azores, a father who required a cane because of gait instability, a sister with "Parkinson's Disease," and a daughter who had recently been diagnosed as having Azorean disease (Case 2). The physical examination was normal. The mental status was normal. Spastic dysphonia interfered with communication, but swallowing was not impaired. The left eye was adducted, and there was limitation of abduction of both eyes. Vertical gaze was preserved. There was marked akinesia and bradykinesia. Mild distal wasting was present in the hands. Strength was normal except for severe weakness of all calf muscles bilaterally. The right Babinski reflex was equivocal, while the left great toe went up with plantar stimulation. Tone was normal. There was a resting tremor of both legs. The patient could not walk without assistance. On standing, she had a stooped posture and fell forwards or backwards. With assistance she walked with a narrow base, stooped posture, and small steps typical of parkinsonism.

During the following year, the patient developed mild titubation of the trunk, mild resting tremor of the hands, mild proximal leg weakness,

severe distal weakness, a right sixth nerve palsy, and increased left Babinski reflex.

Comment: This case is characteristic of the Parkinsonian-motor neuron form of Azorean disease. The eye movement abnormalities, typical of this disorder are never seen with either Parkinson's Disease or Amyotrophic Lateral Sclerosis (ALS), and are not typical of those seen in Olivopontocerebellar Atrophy (OPCA).

Case 2. At age 35 this woman, the daughter of the above patient (Case 1), was evaluated at another hospital because of a four-year history of falling backwards. As this progressed in severity, she noted weakness in her legs, increased problems with balance, arm weakness, and occasional urinary and fecal incontinence. She was diagnosed by one neurologist as having multiple sclerosis (MS) and by another as having hereditary spastic paraparesis. Her physical examination was normal. Her speech and mental status were normal. Cranial nerves were normal except for absent upgaze and inability to converge. She had mild arm weakness bilaterally and mild left leg weakness. Sensory examination was normal to pinprick, touch, vibration, and proprioception. Cerebellar testing revealed mild dysmetria with past pointing in the arms and gross ataxia of the legs. Marked truncal ataxia was present, and she fell backwards on Romberg testing. Although she could walk on her heels and her toes, she had a wide base and could not tandem walk. Her deep tendon reflexes were increased everywhere except for ankle reflexes, which were absent. The left side had a positive Babinski reflex. Laboratory tests included normal spinal fluid (routine studies plus multiple sclerosis studies), normal barium swallow, normal visual evoked responses, borderline slowing of motor and sensory nerve conductions in the leg, mild atrophy of the cerebellar vermis on magnetic resonance imaging, normal blood chemistries (SMA6), complete blood count (CBC) and electrocardiogram (EKG).

Comment: This patient developed a neurologic problem that most commonly would be caused by multiple sclerosis, namely a combination of cerebellar and corticospinal tract abnormalities. Nystagmus, however, was absent. The family history and the absence of supportive laboratory studies for diagnosing MS make Azorean Disease more likely. Not typical of Azorean Disease however, is the presence of urinary and fecal incontinence. Of interest, while this patient's mother had parkinsonism as her major problem, this patient suffered primarily from cerebellar and pyramidal tract dysfunction without evidence of

basal ganglia abnormalities.

Case 3. This 57-year-old man, whose parents were both born in the Azores, developed a progressive gait disorder over the preceding three years and dysarthria for two years. The patient's father died at age 57, and his mother in her seventies. He had four siblings and two children. No other family member is known to have the disorder, but two siblings died in their forties in accidents, and none have been examined. He had been a heavy weekend alcohol drinker, but had stopped ten years ago. There was an unclear history of a possible right hemisphere stroke. A brain computed tomography (CT) scan with and without contrast was normal two years before. The physical examination was normal. His mental status was normal except for a spastic dysphonia and low amplitude voice. Cranial nerves were normal aside from a mild right ptosis without miosis. No nystagmus was present. The motor examination revealed moderate akinesia and bradykinesia, with increased tone throughout and severe spasticity in the arms and legs and occasionally the arms. Reflexes were markedly increased, and Babinski's reflex was present bilaterally. There was mild weakness in the deltoid muscles but wasting was present distally. The sensory examination was normal. The gait was narrow based and extremely slow and unsteady. He had a simian stoop and no arm swing. Leg movements induced leg clonus. He could walk using a walker with small shuffling steps but was very slow.

Comment: This patient of Azorean ancestry has a progressive disorder of the extrapyramidal and pyramidal systems, but without gait ataxia or nystagmus. Thus, he lacks one of the cardinal features of this disorder in addition to having a late onset and no family history. If his biological father was not his social father, or if the father had mild unrecognized disease, then the lack of an affected parent or sibling would be explained. It is quite possible that the gait disorder initially was ataxic, but to only a mild degree, which later was masked by the parkinsonism and severe spasticity which became the salient features of this illness. The diagnosis will be determined by the course of this illness in his offspring.

Discussion

This review was prompted by concern that the diagnosis was not being recognized in our region. Case 3, described above, most likely suffers from Azorean disease, although this is not definite yet. He lives in Providence. It is likely that many pa-

tients and their at-risk offspring either receive their medical care by Rhode Island physicians currently, or will in the near future. There are at least 150 clinically symptomatic individuals with Azorean disease in the southeast Massachusetts region, most from the Fall River area.¹⁴ There have been at least 57 unrelated kindreds identified and an estimated 200 offspring at risk, of whom approximately 50 per cent will become symptomatic. Azorean, or Machado-Joseph, Disease represents a spectrum of an autosomally dominant inherited disease which can be categorized very broadly into three groups: ataxia, ataxia plus a motor neuron syndrome, and ataxia plus motor neuron disease plus parkinsonism. In the most extensive published review,¹³ reporting 138 cases collected, approximately 65 per cent had ataxia with little else, 15 per cent had significant parkinsonism or dystonia with some ataxia and the remaining 20 per cent had a motor neuron (amyotrophic lateral sclerosis) syndrome with ataxia. Although the various subtypes have different median ages of onset, generally in the third decade, children of affected patients with one subtype may have a different subtype and a different age of onset. Siblings not infrequently fall into different categories and patients followed over a period of time occasionally move from one category to another. These findings strongly suggest that this is indeed a single disease with a variable phenotypic expression.

The course of the disease is similarly variable. A retrospective analysis of dead subjects¹³ revealed an average duration of symptoms of 15.6 years. The average duration of symptoms in the 138 cases examined was 9.2 years. It is probable that death, when due to the illness, occurs secondary to aspiration or problems such as decubital ulcer or catheter related sepsis, which arise as a result of immobility.

Only nine cases¹² have been published with autopsies, so that the amount of information available for clinico-pathological correlation is limited. Gait ataxia appears to be due to degeneration of Clarke's column in the spinal cord and in the vestibular nuclei, which are common lesions, rather than to cerebellar lesions. Some cases have shown mild degeneration in pontine and cerebellar (dentate) nuclei, but these have had limb ataxia. The progressive external ophthalmoplegia is due to degeneration of the abducens nuclei and thus is a nuclear ophthalmoplegia which cannot be overcome by the oculocephalic (doll's eyes) maneuver. The distal muscular atrophy and fasciculations are caused by degeneration of the an-

terior horns of the spinal cord, but little demyelination has been seen in the corticospinal tracts to explain the spasticity and positive Babinski reflexes. The parkinsonian features are caused by degeneration in the substantia nigra. Changes in the striatum when present have been minor, and in one case even disputed by neuropathologists reviewing the same slides.^{15, 16} A recent report documents mild to moderate peripheral nerve changes in all patients biopsied.

Thus the disease has a pathological expression that varies as does the clinical expression. There is no definitive pathological change to mark the disease such as a neurofibrillary tangle or a Lewy body. While the disease clinically greatly resembles the olivopontocerebellar atrophy disorders, pathologically there is no involvement of the olive and little of the cerebellum and pons. This disease should be classified as a "multi-system atrophy," meaning that multiple discrete parts or systems of the nervous systems are affected (Clarkes' nucleus, vestibular nuclei, substantia nigra, anterior horns, oculomotor nuclei).

There is no known method of arresting progression of the disease or of treating the gait disorder. There is anecdotal evidence to suggest that L-DOPA is of some benefit in treating the parkinsonism which may develop.¹³ Genetic studies to date have demonstrated that the gene for Azorean Disease is not on chromosome 6, where the HLA complex and the gene for some of the olivopontocerebellar atrophies lie,¹⁷ is also not on the end of chromosome 1,¹⁷ and is unrelated to the gene for Huntington's Disease.¹⁸ Clinical studies on genetic diseases in general have indicated that about 10 per cent of patients studied have negative family histories for the disorder, because the biological father is not the apparent father. This, or a natural mutation, may explain Case 3 above. Physiologic studies of extraocular movements, evoked responses, and nerve conduction studies have not shown any promise in predicting whether at-risk individuals will develop the disease.^{19, 20}

Frequently this disease is not recognized and is misdiagnosed as multiple sclerosis, parkinson's disease, or ALS. It is important to diagnose the disorder correctly for several reasons. The course is considerably more benign than ALS and does not fluctuate like MS. It is hereditary, so that the family requires genetic counseling. A national support group exists to provide information and support and to give reassurance that the patient is not alone. In addition, genetic research on this disease is active, and it is possible that within the

next few years a genetic marker will become available so that asymptomatic offspring of affected individuals will be able to learn, in advance of having children, whether they themselves will be affected or not.

Summary

A hereditary disease affecting Azorean descendants in the United States is found primarily in southeastern Massachusetts and northern California. Known as Machado-Joseph Disease or Azorean Disease, this adult-onset autosomal dominant degenerative condition of the nervous system causes gait ataxia plus a wide range of other abnormalities including parkinsonism, amyotrophic lateral sclerosis, and ophthalmoplegia. This disorder has been under-recognized in our region and is therefore reviewed. Illustrative case histories are provided.

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Appendix

Physicians who believe they have patients with this disorder should contact Patrick MacLeod, MD, Division of Medical Genetics, Department of Paediatrics, Queen's University, 20 Barrie Street, Kingston, Ontario, Canada K7L 3J6. Dr. MacLeod is trying to identify a genetic marker for this disease and visits Fall River annually to collect information. The Joseph's Disease Foundation address is: PO Box 2550, Livermore, California 94550.

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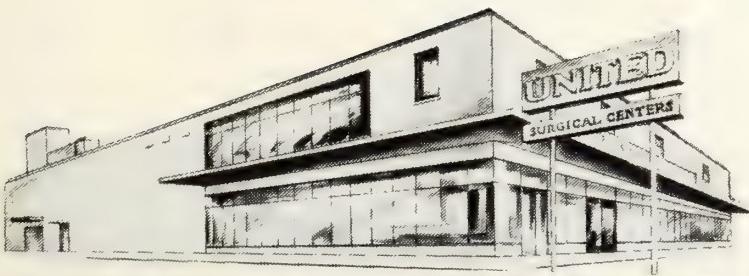
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Rocky Mountain Spotted Fever In Rhode Island: Case Report And Review Of Its Occurrence During The Past Ten Years

Early Recognition of this Rickettsial Disease Mildly Endemic in Rhode Island is Important

Vipul Singh, MD
Steven M. Opal, MD

Rocky Mountain spotted fever (RMSF) is a tick-borne rickettsial disease, which may produce severe potentially life threatening infection. The disease is transmitted by *Dermacentor spp* ticks and is endemic along the east coast. The majority of the over 700 cases which occur annually in the United States are found in the summer months when tick activity is greatest.

In the case described herein, a severe episode of Rocky Mountain spotted fever developed in a previously healthy, young adult in Newport County, Rhode Island. This infection is uncommon in Rhode Island, but has been observed in 17 cases during the past 10 years. The epidemiology and clinical characteristics of RMSF in Rhode Island are briefly reviewed.

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Case Report

A previously healthy 23-year-old man was admitted to Memorial Hospital of Rhode Island with a chief complaint of fever up to 40.5°C during the preceding week. A remittent temperature pattern was described in addition to several episodes of severe shaking chills. He also complained of severe and diffuse myalgia, arthralgia, and a pounding frontal headache. A fine rash was noted on the day of admission. He denied any photophobia, stiff neck, respiratory symptoms, or gastrointestinal complaints. He denied recent contact with persons with febrile illnesses. There was no exposure to pets or other animals, and he had not traveled outside Rhode Island over the past year. He denied intravenous drug abuse, homosexual activity, or recent heterosexual contact. On repeated questioning he did recall a history of tick attachment on his left thigh two weeks prior to the onset of his illness. The tick was discovered after visiting a wooded area in Newport County. The patient had self-administered penicillin at a dose of 250 mg four times a day for four days without any improvement in his symptoms.

Physical examination revealed a toxic appearing, diaphoretic male with a temperature of 39.9°C, pulse of 124/min, respiratory rate of 34/min, and blood pressure of 100/60.

His peripheral pulses were bounding, and his sensorium was normal. Mild periorbital edema was noted. His cardiopulmonary examination was unremarkable. The abdomen was soft without masses or hepatosplenomegaly. Rectal exami-

nation was unremarkable. Neurological examination was normal. A fine macular rash with scattered petechiae was found on the volar aspect of his wrists, and ankles, and anterior thorax. Musculoskeletal examination revealed diffuse tenderness but no localized swelling. There was no synovitis or peripheral edema.

Admission laboratory examination included a white blood count (WBC) of $8 \times 10^9/L$ (8000/mm³) with a shift to the left. The hematocrit was 36.3 per cent with normal red blood count (RBC) indices. The platelet count was $92 \times 10^9/L$ (92,000/mm³). Chest radiograph was normal as was the urinalysis. Serum electrolytes were normal except for a sodium of 128 mmol/L and creatinine of 1.5 mg/dl. Blood and urine cultures were obtained and were subsequently reported as negative. A clinical diagnosis of RMSF was considered in addition to other infectious diseases, including meningococcemia or infective endocarditis. The patient was treated with intravenous chloramphenicol at a dose of 50 mg/kg/day in four divided doses. Other laboratory studies such as liver function studies and serologic studies for the Epstein-Barr virus and cytomegalovirus and syphilis were unremarkable.

On the second hospital day, the patient became dyspneic and developed inspiratory rales. Chest radiograph revealed increased vascular congestion and a pulmonary infiltrate at the right base. He subsequently developed a right-sided pleural effusion as well. Sputum examination was unremarkable. A skin biopsy was performed and direct fluorescent antibody staining revealed evidence of *Rickettsia rickettsii*. This provided presumptive evidence of RMSF. The Weil-Felix agglutinins were positive for RMSF at a titer of 1:80 for Proteus OX 19; IgM antibody against *Rickettsia rickettsii* was positive by IFA at 1:8; IgG-IFA was positive at a titer of 1:128. A two-dimensional echocardiogram demonstrated a small posterior and moderate anterior pericardial effusion without signs of pericardial tamponade. Wall motion was hyperdynamic and mild mitral and pulmonic regurgitation was present. No valvular vegetations were noted.

Patient began to improve with a gradual defervescence and decrease in myalgias and headache. A follow-up chest x-ray study showed considerable clearing of the right basal infiltrate, and his hyponatremia resolved. After 48 hours of intravenous chloramphenicol, the patient was switched to oral tetracycline at a dose of 750 mg every six hours. He continued to do well and was discharged from the hospital on the 12th day.

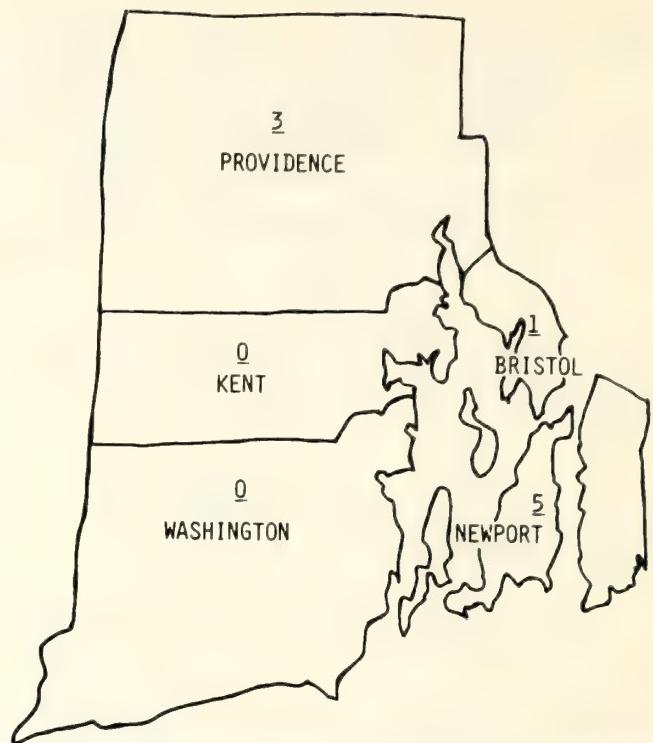


Fig 1. Seasonal occurrence of Rocky Mountain spotted fever in Rhode Island during the years 1976-1986.

Retrospective Case Review

During a 10-year study period from 1976 to 1986, 17 serologically confirmed cases of RMSF were reported to the Rhode Island Department of Health. This represents 0.2 per cent of all cases of RMSF in the United States during the ten-year period. Nine patient charts were available for review from the records of the Department of Health. The average age of the patients was 29 ± 17.7 years (range 4-61) with male:female ratio of 2:1. The majority of the cases came from Newport County (5/9), followed by Providence County (3/9) (Figure 1). Similar to the national experience, most cases occurred in the months of June and July (Figure 2).

A history of tick attachment was obtained in six patients, and two others recollect ticks within two weeks of their illness, but denied tick attachment. All nine patients had fever, myalgia, and headache. However, only two of nine (22 per cent) developed characteristic skin rash involving palms and soles. The characteristic rash developed six days after the onset of fever leading to initial diagnostic confusion.

The attending physicians suspected the correct diagnosis in only six of nine cases upon initial presentation. Other diagnostic considerations included bacterial meningitis, gram negative sepsis,

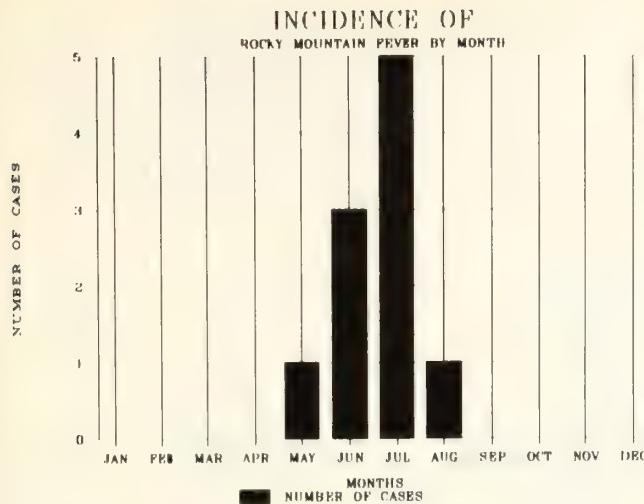


Fig 2. Geographic location of nine cases of Rocky Mountain spotted fever occurring in Rhode Island during the years 1976-1986.

viral exanthems, and drug eruptions. Specific therapy with tetracycline, chloramphenicol, or both, was curative in all patients. No deaths were reported, and eight of nine patients were hospitalized for an average of seven days.

Discussion

RMSF is the most frequently reported arthropod-borne disease in the United States, with an increase in reported cases from 199 in 1959 up to over 1000 cases in 1977.¹ *Rickettsia rickettsii*, the causative agent, grows in the nucleus as well as in the cytoplasm of infected cells. The vector for humans is the tick *Dermacentor andersoni*, the wood tick in the western United States and *Dermacentor variabilis*, the dog tick in the eastern United States.² Ticks acquire non-lethal lifelong infection either by feeding on an infected small animal or by transovarial transmission from infected adult female ticks.³ The route of infection is generally through the skin, as the rickettsiae are injected via the tick's mouth parts. After local proliferation at the inoculation site, the rickettsiae spread hematogenously. The principal pathologic feature of this disease is disseminated focal infection of the small blood vessels (capillaries, arterioles, and venules) of the skin and, to a lesser extent, of other organs including the brain, heart, lung, and kidneys. The rickettsial organisms invade, multiply, then disrupt endothelial cells of the vascular system resulting in necrosis, hypertrophy, and endothelial proliferation. Infection may extend to all layers of the vessel wall, causing necrosis of the media. A typical perivascular inflammatory response develops, with a

polymorphonuclear and monocytic cellular response. Immunity to the infecting organism following recovery is solid and long-lasting. Yet, the basis for immunity remains incompletely understood.

RMSF occurs primarily in the summer months when tick activity is greatest. The preponderance of male patients may reflect increased occupational or recreational exposure to tick infected areas. A history of tick bite can be elicited in many, but not all patients, and the absence of such a history is often misleading. Persons without a recognized history of tick exposure regularly make up 10-20 percent of cases of RMSF.^{4,5} In the current series from Rhode Island, only six of nine patients gave a history of tick attachment. The incubation period averages about seven days (range 2-14 days).

The typical infection is sudden in onset with severe headache, chills, myalgia, and prostration. Nausea, vomiting and abdominal pain may be present. Fever may reach 40°C within the first two days and remain elevated for more than two weeks. Severe hyperthermia greater than 41°C is an ominous sign in RMSF.

The characteristic rash appears on about the fourth day consisting of pink 2-5 mm macules which first appear on the wrist and ankles and then extend to palms, soles, trunk, and mucous membranes. In 48-72 hours they become darker, papular, and eventually petechial. Occasionally the rash becomes hemorrhagic and will coalesce. In many patients a rash may not develop. In Rhode Island, only 22 per cent of patients with RMSF developed a typical rash. In a large national survey of 485 cases (from 1979-1981) only 34 per cent showed a characteristic rash.⁶ It is important to be aware that the rash is generally absent at the onset of the clinical illness. The average duration of symptoms prior to development of skin lesions was six days in this series from Rhode Island.

Headache is often present in 40-60 per cent of patients. It can be quite severe and may dominate the clinical presentation. Viral or bacterial meningitis or subarachnoid hemorrhage may be the initial diagnostic impression in patients with RMSF. Mild to moderate myalgia is seen in 51-83 per cent of patients and can be very severe in 25-47 per cent of cases.⁷ All of the patients in the current series complained of headache and myalgia.

Complications, which can be life-threatening, may occur. In a series of 262 patients, clinical complications occurred in nine per cent of cases,

including psychiatric problems, renal failure, intracranial bleeding, gangrene, neuropathy, syndromes of inappropriate secretion of antidiuretic hormone, and respiratory failure.⁷ Other complications known to occur are disseminated intravascular coagulation (DIC), myocarditis, shock, seizure, and coma. Fatal cases are associated with incorrect initial diagnosis; delay in treatment; absence of the classical triad of fever, rash, and history of tick exposure; splenomegaly; edema; meningismus; pneumonitis; cardiac complications; hyponatremia; hypoalbuminemia; renal failure; thrombocytopenia; DIC; and hepatic failure.¹¹ Fortunately only one patient in our series developed complications of hyponatremia, hypoalbuminemia, and azotemia. The outcome was favorable in this patient as in all others in Rhode Island during the past decade. The overall mortality rate in the United States in 1986 was 3.0 per cent.¹²

The early diagnosis of RMSF depends upon clinical awareness. In a national study the correct diagnosis was made in 41 per cent of initial visits.⁵ This is similar to the experience in Rhode Island (six of nine cases). In the first three days of illness, only three per cent of patients in the United States have the classic triad of fever, rash, and history of tick exposure. Screening laboratory tests such as Weil-Felix agglutinins are non-specific and insensitive and are frequently useful only in making a retrospective diagnosis. Other tests such as microimmunofluorescence, latex agglutination, and complement fixation studies are more specific yet; confirmation may require two to three weeks.¹³ Direct fluorescent antibody (DFA) staining of skin biopsy specimens is an accurate and reliable method of early diagnosis.⁸

Early diagnosis and treatment are important to prevent a fatal outcome, as it has been shown that the mean interval from onset of symptoms to initiation of therapy was 5.33 days for fatal cases compared with 3.56 days for non-fatal cases.⁶ Treatment consists of tetracycline or chloramphenicol therapy. The beta lactam agents such as the penicillins and cephalosporins are totally ineffective.

Conclusion

Rocky Mountain spotted fever has occurred sporadically in Rhode Island with an incidence of 0.2 cases per 100,000 per year during the past 10 years. The disease should be considered in febrile patients with myalgias and headache presenting in the summer months, even in the absence of a characteristic skin rash. The classical

triad of fever, rash, and tick exposure is frequently lacking at initial presentation. Delay in appropriate therapy can lead to significant morbidity and mortality.⁹ Prompt clinical recognition and institution of therapy are of paramount importance in this potentially fatal disease.

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Twenty-nine control infants and the first ten infants who subsequently died of sudden infant death syndrome (SIDS) were analyzed for the relation between the Q-T interval and changes in heart rate on electrocardiograms. The infants who later died of SIDS showed weaker dependence of the Q-T interval on changes in heart rate than the normal controls. An inappropriately low correlation between the Q-T interval and changes in heart rate was distinguishable in five of the ten infants who died of SIDS. Blocked depolarization or a predisposition to ventricular reentry and fibrillation is the result of decreases in the

R-R interval that are not accompanied by an appropriate decrease in the Q-T interval.

• • •

The pain of rheumatoid arthritis may be reduced through injections of a drug used to control high blood pressure. This according to researchers at the University of California in San Francisco, from a recent *Arthritis Today*. A significant reduction in pain after only one treatment was reported by people given injections of the drug guanethidine. This improvement in pain, stiffness, tenderness and grip strength lasted as long as two weeks. Guanethidine administered in larger doses blocks the sympathetic nervous system — preventing the nerves from sending signals to the brain that a joint is in "pain." The researchers, Dr John D. Levine and his colleagues, stress the importance of injecting the drug directly into the damaged joint. Otherwise, the person receiving treatment would feel light-headed from low blood pressure. Further studies are underway for this medication. It is not approved by the Food and Drug Administration for use in treating arthritis, and researchers stress that use of guanethidine should be postponed until more is learned about the drug and its effects on joint inflammation.

• • •

According to Philadelphia researchers, examination of the hip area can be very helpful in early diagnosis of osteoporosis. Previously, the only diagnosis of osteoporosis was by X-ray which can only detect the disease after it has reached the most advanced stages. Dual and single photon absorptiometry, currently used types of bone-scanning techniques, can detect very small changes in the amount of bone. Researchers measured hips, lower backs and wrists in 149 people using this equipment. Measurement of the hip detected a loss of bone density not yet apparent in the wrists or back.

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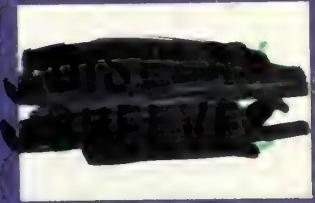
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Country	ADR Reports/ Thousand Physicians	ADR Reports/ Million Population
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Sweden	167.3	334.7
United Kingdom	163.3	262.5
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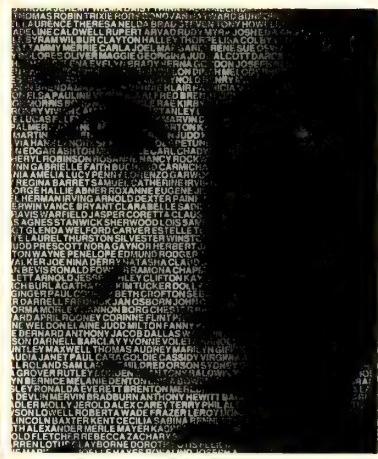
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In a recent survey, 4,120 participating physicians gave us their views¹ on INDERAL LA in the treatment of hypertension, angina and migraine.

INDERAL LA is their preferred beta blocker

...of the nearly three out of four physicians responding to the questionnaire, an impressive 97% rated INDERAL LA good to excellent for overall performance. Virtually all cited efficacy, tolerability, long-term cardiovascular protection and once-daily convenience as important factors in their choosing to prescribe INDERAL LA.

INDERAL LA promotes patient compliance

...Virtually every responding physician rated patient satisfaction with INDERAL LA to be as good as, or better than, other beta blockers.

Like conventional INDERAL Tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree and bronchial asthma.

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LONG ACTING
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60, 80, 120, 160 mg

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Please see next page for brief summary of prescribing information.

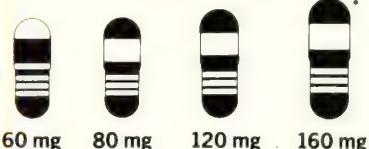
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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® LA brand of propranolol hydrochloride (Long Acting Capsules)

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. Inderal is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by Inderal, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Inderal LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with Inderal LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of Inderal Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

Inderal LA should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to Inderal LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, Inderal LA has been therapeutically equivalent to the same mg dose of conventional Inderal as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. Inderal LA can provide effective beta blockade for a 24-hour period.

INDICATIONS AND USAGE. **Hypertension:** Inderal LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. Inderal LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: Inderal LA is indicated for the long-term management of patients with angina pectoris.

Migraine: Inderal LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: Inderal LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. Inderal LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. Inderal is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with Inderal.

WARNINGS. **CARDIAC FAILURE:** Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitized and/or treated with diuretics, and the response observed closely, or Inderal should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of Inderal therapy. Therefore, when discontinuance of Inderal is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If Inderal therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute Inderal therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Inderal should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Inderal (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta blockers should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid function tests, increasing T₄ and reverse T₃, and decreasing T₃.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Propranolol should be used with caution in patients with impaired hepatic or renal function. Inderal (propranolol HCl) is not indicated for the treatment of hypertension emergencies.

Beta-adrenoceptor blockade can cause reduction of intraocular pressure. Patients should be told that Inderal may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if Inderal (propranolol HCl) is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbital, and rifampin accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and lidocaine have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T₃ concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related teratogenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

PREGNANCY: Pregnancy Category C. Inderal has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. Inderal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: Inderal is excreted in human milk. Caution should be exercised when Inderal is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia, congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasisiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctiva reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. Inderal LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from Inderal Tablets to Inderal LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. Inderal LA should not be considered a simple mg-for-mg substitute for Inderal. Inderal LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION — Dosage must be individualized. The usual initial dosage is 80 mg Inderal LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS — Dosage must be individualized. Starting with 80 mg Inderal LA once daily, dosage should be gradually increased at three- to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE — Dosage must be individualized. The initial oral dose is 80 mg Inderal LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, Inderal LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS — 80-160 mg Inderal LA once daily.

PEDIATRIC DOSAGE — At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Reference:

1. Data on file, Ayerst Laboratories.

D7295/188



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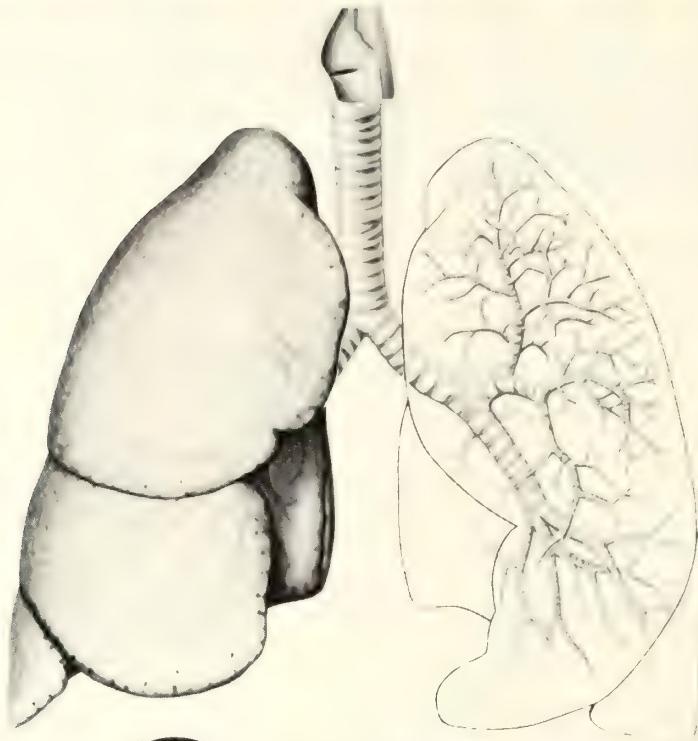
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Cover: Graph depicting physician reporting of adverse drug reactions in various countries courtesy of Rhode Island Department of Health. See page 179.

Consider the causative organisms...



Ceclor® cefaclor 250-mg Pulvules® t.i.d. offers effectiveness against the major causes of bacterial bronchitis

Haemophilus influenzae and *Streptococcus pneumoniae*
(ampicillin-susceptible and ampicillin-resistant)

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Ceclor® (cefaclor)

Summary. Consult the package literature for prescribing information.

Indication: Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β -hemolytic streptococci).

Contraindication:
Known allergy to cephalosporins

Warnings:

CECLR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY. POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS.

Administer cautiously to allergic patients. Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:

- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.
- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] or the above skin manifestations accompanied by arthritis, arthralgia and, frequently, fever]: 1.5%; usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.
- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertension, dizziness, and somnolence have been reported.
- Other eosinophilia, 2%; genital pruritus or vaginitis, less than 1%; and, rarely, thrombocytopenia.
- Abnormalities in laboratory results of uncertain etiology
- Slight elevations in hepatic enzymes
- Transient fluctuations in leukocyte count (especially in infants and children)
- Abnormal urinalysis; elevations in BUN or serum creatinine
- Positive direct Coombs' test
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinistest® tablets but not with Tes-Tape® (glucose enzymatic test strip, Lilly). [061787L]

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

ousness, insomnia, confusion, hypertension, dizziness, and somnolence have been reported.

• Other eosinophilia, 2%; genital pruritus or vaginitis, less than 1%; and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology

- Slight elevations in hepatic enzymes
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- Positive direct Coombs' test
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EDITORIAL

AIDS Testing and The Health Department Legislation

Recently Doctor Jonathan Mann, head of the World Health Organization's Acquired Immune Deficiency Syndrome (AIDS) program warned the White House AIDS commission that we are still in the early stages of a global epidemic. "While it has become fashionable," he stated, "to reassure and state that AIDS will never threaten large populations, we believe that virology, immunology, sociology, and epidemiology require us to take the long view, and a more somber view."

The recently introduced omnibus AIDS bill, representing the combined efforts of the Director of Health, H. Denman Scott, MD, and Senator James D'Ambra and other influential senators, addresses these issues in a forthright manner. It is timely, reasonable, and farsighted. If enacted, it will make Rhode Island first among states in the enactment of this essential legislation and echo the progressive role in public health practices played by Doctor Scott's distinguished predecessor, Charles V. Chapin.

Although the legislation touches upon some sociological and political matters, its primary thrust has to do with mandatory and routine testing for Human Immunodeficiency Virus (HIV) — the AIDS virus — under certain circumstances. The categories in which testing will be required are:

1. Every person admitted as an inpatient for care and treatment in any hospital.
2. Any person attended by a physician or health care provider for a suspected transmitted disease.
3. Any person seeking prenatal or family planning services.
4. Any person attending a facility for drug abusers.
5. Every applicant for a marriage license.
6. Any person admitted to the Adult Correctional Institute.
7. Any person convicted of prostitution or lewdness.
8. Any person convicted of a violation of the

Uniform Controlled Substances Act.

There are exceptions to the mandatory provisions and elaborate clauses to protect "confidentiality." "No person may be tested for the AIDS virus," according to the bill, "where the test result can be identified with a specific individual, unless he or she has given their [sic] consent . . . after discussion of implications of the test with a qualified professional."

These provisions are analogous to those long in effect for Syphilis. Hospital testing is no longer routine for that disease and Syphilis now is a treatable disorder. But the logic which applied for several generations, is more than applicable to AIDS, which thus far is incurable.

At this writing the legislation has passed the State Senate and is pending in the House of Representatives. Controversy has arisen over a questionable provision in the bill which allows owners of residences with six or fewer housing units to refuse to rent to persons with the AIDS virus, or "perception of same." This provision is or should be, negotiable, and the legislation should not be allowed to founder over this red herring.

Several civil rights and special interest groups are opposed to mandatory testing under any circumstances and also raise over-stated questions regarding confidentiality. Their views are short-sighted, and the argument that the \$2.5 million dollar a year cost of administering the bill should be applied to "education" is really naive. Education is extremely important and should be utilized to the maximum extent, but it is a long-term process and will not effect appreciably the epidemiological emergency which is upon us.

We strongly support the "Act Relating to Health and Safety, AIDS Testing, Confidentiality, and Discrimination." We vigorously urge the General Assembly to adopt this important legislation and trust that it will be well on the way to adoption when this Editorial appears in print.

Seebert J. Goldowsky, MD

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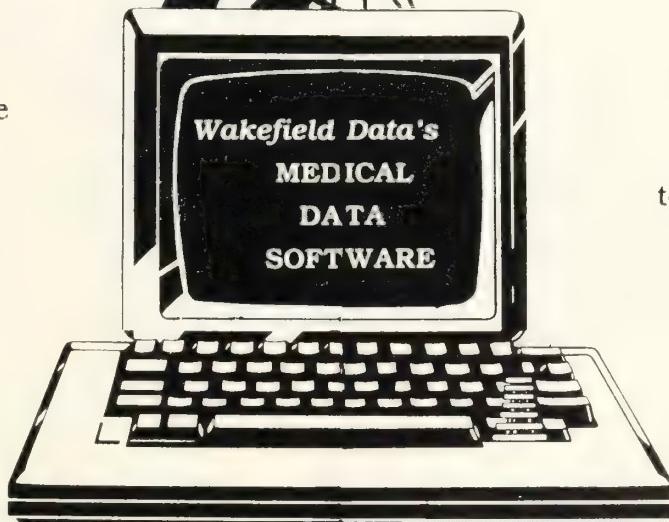
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BRIEF SUMMARY

CONTRAINDICATIONS

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PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonspecific in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE

There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

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CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1712-49). Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 bracketed by C's on the other.

Issued 1/87

References:

1. Korman MG, Shaw RG, Hansky J, et al: *Gastroenterology* 80:1451-1453, 1981
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4. Marks IN, Wright JP, Gilinsky NH, et al: *J Clin Gastroenterol* 8:419-423, 1986
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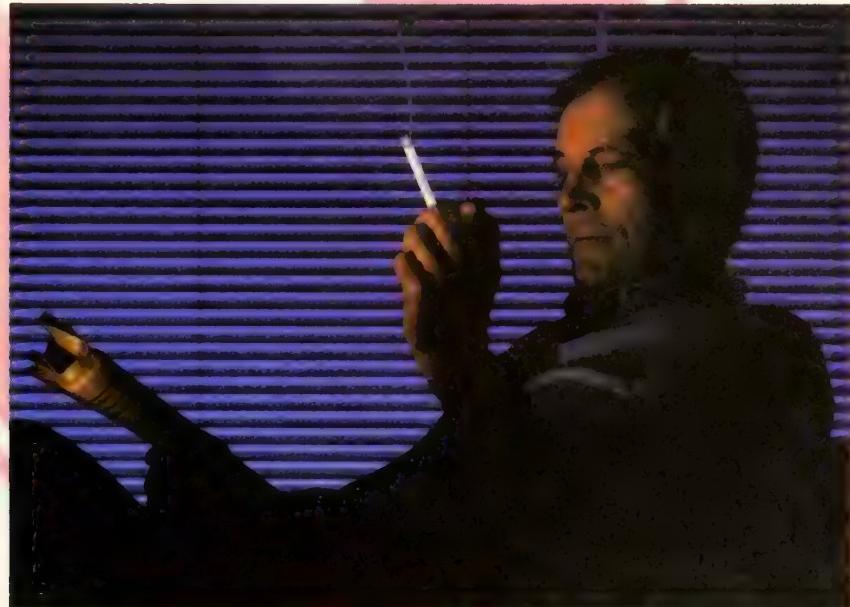
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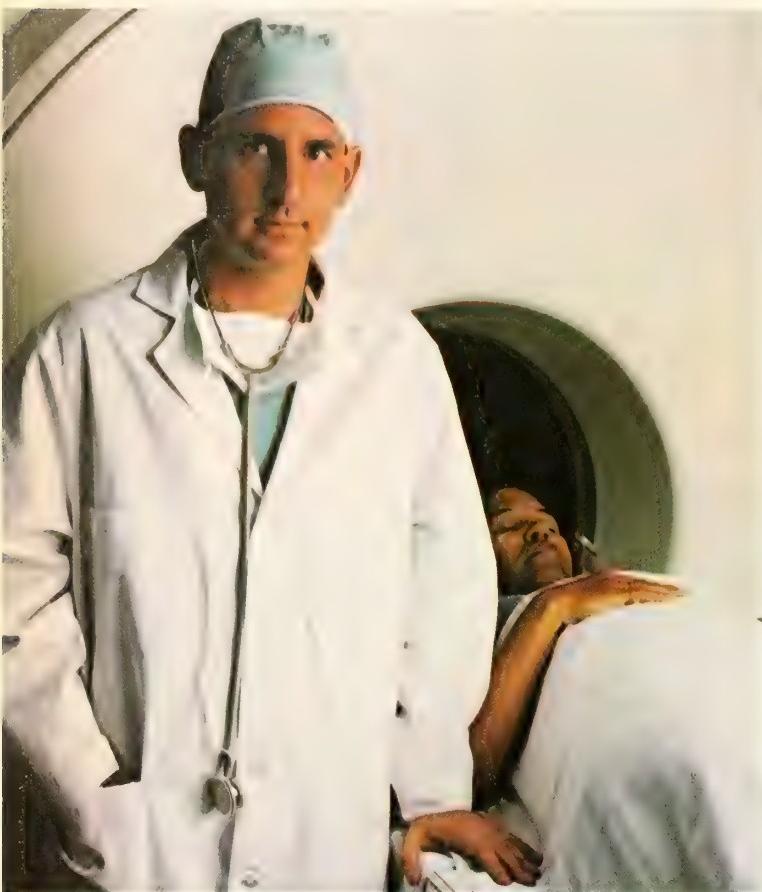
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ALLAN J. HAMILTON, M.D.

Neurosurgical Resident and Research Fellow,
Massachusetts General Hospital, Boston, Massachusetts.
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EDUCATION Ithaca College, B.A. (Magna Cum Laude);
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CONTINUING EDUCATION Neurology and Neuro-
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OUTSTANDING ACHIEVEMENTS Olsen Memorial
Fellowship, National Masonic Medical Research Foundation;
Albert Schweitzer Fellowship, International Albert Schweitzer
Foundation; Harvard Medical School Cabot Prize for Best
Senior Thesis; recently published article, "Who Shall Live
and Who Shall Die" in Newsweek Magazine.

■■■ The work I'm doing in the Army Reserve fits perfectly with my academic research interests in civilian life. The Army is very concerned with the effects of high-altitude cerebral edema, which is a mirror model of cerebral hypoxia, something I deal with every day in our neurosurgical intensive care unit. I couldn't ask for a smoother transition. And that's true for a lot of Reserve physicians. All we really do is change our clothes, not our mindset.

"Some of the projects the Army is undertaking are on the cutting edge of research. For example, I'm currently involved in developing for the Army a prototype of a non-invasive intracranial pressure-monitoring device that we hope will allow us to measure pressure changes as the brain swells—without drilling holes in the skull. If we can get our design to work, such a device could revolutionize high-altitude medicine as well as civilian neurosurgical care.

"The quality of medicine and the caliber of people I've been associated with in the Army Reserve are, without question, equal to civilian hospitals. In fact, I'm giving serious consideration to applying for an active duty academic position in Army Medicine when my residency ends at Massachusetts General. ■■■

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IMPORTANT: SUBMISSION OF A REPORT DOES NOT NECESSARILY CONSTITUTE AN ADMISSION THAT THE DRUG CAUSED THE ADVERSE REACTION				
PATIENT INITIALS (Optional) A.D.R.	AGE (years) 54	SEX <input checked="" type="checkbox"/> MALE <input type="checkbox"/> FEMALE	DATE OF REACTION ONSET 12 Oct. 1986	
DESCRIBE REACTION(S) (Signs, symptoms, diagnoses, course and abdomen) JAUNDICE			CHECK ALL APPROPRIATE TO REACTION <input type="checkbox"/> DIED <input checked="" type="checkbox"/> TREATED WITH RX DRUG <input checked="" type="checkbox"/> INPATIENT HOSPITALIZATION <input type="checkbox"/> SEVERE OR PERMANENT DISABILITY <input type="checkbox"/> EMERGENCY ROOM TREATMENT <input type="checkbox"/> TREATMENT IN PHYSICIAN OFFICE <input type="checkbox"/> NONE OF THE ABOVE	
SUSPECTED DRUG(S) (Trade Name is preferred; if a generic product, give manufacturer's name or N.R.C. for vaccines, biologics) HYPERTENSION				
REASON FOR USE OF DRUG(S) HYPERTENSION	ROUTE P.O.	TOTAL DAILY DOSE 100mg.	DATES OF ADMINISTRATION 9 Sept.- 12 Oct. '86	
OTHER DRUGS TAKEN CONCOMITANTLY (Exclude those used to treat reaction) None				
OTHER RELEVANT HISTORY (e.g., Concomitant Diagnoses, Pregnancy, etc.) None				
PHYSICIAN NAME AND TELEPHONE NUMBER J. Doe, M.D. 277-2550				
ALSO REPORTED TO MANUFACTURER <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO				
Confidential				



**The Adverse Drug Reaction
Reporting Project**
of the Rhode Island Department of Health

To report an ADR by phone, call 456-ADRS weekdays between 9 and 5. To receive mailing forms and additional information, call the Health Department at 277-2901.

Adverse Drug Reaction Reporting Systems: The United Kingdom and the United States

Rhode Island is Participating in a Project to Improve Individual Physician's Understanding of the Vital Importance of Reporting

H. Denman Scott, MD, MPH

Ann Thacher, MS

Sara E. Rosenbaum, PhD

William J. Waters, Jr., PhD

Marilyn Green, BA

The use of drugs, even in recommended doses, may be associated with adverse effects. According to Karch and Lasagna,¹ studies which attempt to determine the incidence of adverse drug reactions (ADRs) may be incomplete, unrepresentative, uncontrolled, or lacking criteria, making

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William J. Waters, Jr., PhD is Assistant Director for Health Policy, Rhode Island Department of Health, Rhode Island.

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a true determination of incidence difficult to ascertain. An extensive review of the literature performed by Karch and Lasagna revealed that 1.5 to 35 per cent of hospitalized patients experience an ADR and that up to 0.3 to 3 per cent of hospital admissions may be attributable to ADRs. A more thorough understanding and knowledge of individual ADRs may help to reduce these numbers.

Physicians in the United States (US) are an important source of information for early warnings of adverse reactions. Although only one per cent of ADR reports received by the Food and Drug Administration (FDA) in 1970 were direct physician reports, these reports represented 24 per cent of all new verified adverse reactions for that year. And yet physicians in the United States underreport ADRs both in absolute terms and relative to physicians in many other countries.²⁻⁵

Based on a recent survey of Rhode Island physicians,⁵ approximately 36,000 ADRs of all types occurred in Rhode Island in 1985; of these, about 2,000 were fatal or severe. Yet for the years 1976 through 1985, the FDA received on average only 55 reports of suspected ADRs each year from Rhode Island physicians.

Though not unique to the United States, this underreporting is more severe here than in many other Western countries (Table 1).⁴ For example, in 1983 physicians in the United Kingdom reported 163.3 ADRs per 1,000 physicians. Only

Table 1. Frequency of Adverse Reaction Reports per Thousands of Physicians and Per Million Population

Country	ADR Reports/ Thousand Physicians	ADR Reports/ Million Population
Denmark	187.2	407.6
Sweden	167.3	334.7
United Kingdom	163.3	262.5
New Zealand	141.4	383.2
United States	57.6	147.0

57.6 ADRs per 1,000 physicians were reported in the United States. Furthermore, there were more than 250 ADR reports in the United Kingdom from all sources per million population compared with less than 150 reports per million population in the United States.⁴

In an effort to determine why physicians in the United Kingdom are three times more likely to report ADRs than are their counterparts in the United States, we compared the voluntary spontaneous reporting systems used in both countries. In addition, physician attitudes in each country toward reporting were compared, using the results of our survey of Rhode Island physicians and a study of physicians in the Royal Liverpool Hospital.²

Drug Usage

The increased number of ADR reports from the United Kingdom is not the result of heavier prescribing practices by its physicians. In the United States, physicians prescribe more medications than their counterparts in the United Kingdom.⁴

The FDA's strict drug approval process cannot account for all of the different rates of reporting. Kaitin et al⁶ compared the rates at which the United States and United Kingdom approved new drugs to determine if there were a significant time lag. Of seven classes of therapeutic drugs, the United States lagged behind the United Kingdom in the introduction of cardiovascular agents (seven years) and central nervous system drugs (four years). However, the United States led the United Kingdom in the approval of cephalosporins, and the two countries marketed antibiotics at approximately the same rate. Overall, of 26 new drugs introduced in 1985 in the United States, 18 (69 per cent) had already been marketed outside the United States for an average of 4.2 years.⁷

Level 1

The thalidomide tragedy in the early 1960s was the catalyst to initiate national surveillance efforts in the United States and in the United Kingdom. In both countries the central registries (the FDA in the United States and the Committee on Safety of Medicines [CSM] in the United Kingdom) rely on reports from physicians and pharmaceutical manufacturers to signal early warnings about potentially unsafe drug reactions.

United States. The Division of Epidemiology and Surveillance within the FDA is responsible for collecting, analyzing, and disseminating information about ADRs. The bulk of reports (90 per cent in 1985) are submitted by manufacturers, which have been compelled by law since 1962 to report known ADRs.^{4, 8, 9}

Once received by the FDA, the reports are entered into the computer data base, which already lists more than 280,000 different reports. The serious reports (ie, those involving death, hospitalization, disability, congenital anomaly, or cancer) and those reports received directly from physicians and other health professionals are reviewed individually by a professional reviewer. Problematic ADRs, labeled Monitored Adverse Reactions, are then evaluated further by a team of epidemiologists, drug utilization experts, and others before future action is decided, including possible "Dear Doctor" letters, revisions in product labeling, or possible withdrawal of the drug.^{10, 11}

Reports from manufacturers are made using the FDA's Form 1639. Recognizing that this form with its 25 data elements was cumbersome for individual physicians and in an effort to stimulate direct reporting, the FDA in 1972 simplified Form 1639 to only 13 data elements. The new form is mailed periodically to more than 1 million health care providers with the *FDA Drug Bulletin*, and was also inserted in the back of the 1987 *Physicians' Desk Reference*.¹²

United Kingdom. That physicians in the United Kingdom report ADRs at a higher rate than their US counterparts does not indicate full compliance with the system. Although approximately 100,000 reactions that threaten life or delay recovery are estimated to occur there annually, only 300 to 400 fatal reactions and up to 12,000 non-fatal reactions are reported each year to the Committee.¹³ Furthermore, 84 per cent of physicians in the National Health Service failed to use the system at all between 1972 and 1980.¹⁴

The "yellow card," the reporting form in the United Kingdom, is used by physicians to report directly to the CSM. Yellow cards are also used by pharmaceutical companies, which are required by statute to report all ADRs reported to them. From the time of its inception in 1964, the CSM has assured physicians that information relayed via the card would always be treated confidentially and never be used for disciplinary actions against physicians.⁸

In addition to reporting all serious labeled and nonlabeled reactions, physicians are further requested to report even seemingly insignificant signs and symptoms related to any new drugs. The *Monthly Index of Medical Specialties* and the *British National Formulary*, the prime sources of drug dispensing information for physicians in the United Kingdom, identify these new entities by placing an inverted triangle next to the drug's listing. In determining what constitutes a reportable event, the motto of the CSM is "When in doubt — report."⁸

Beginning in 1976, a slip of yellow paper was added to National Health Service prescription pads to remind doctors to report suspected ADRs. The number of reports registered subsequently jumped from 6,490 reports in 1976 to 11,255 in 1977. Other factors, however, may have contributed to the increase, most notably concern about the failure of the voluntary reporting system to detect the adverse reactions associated with use of practolol.¹⁴

Reports are received by the Subcommittee on Safety, Efficacy, and Adverse Reactions, which collects and assesses each report, determines epidemiological aspects of the report, and when warranted disseminates information to the physician community. The professional staff meets weekly to scrutinize reports and to draw up reaction profiles.

Reaction profiles compare the pattern of reactions to a drug in relation to the pattern of reactions produced by other therapeutically related drugs. Once hazards are identified, the reports are followed up, using more than 200 medical investigators. These investigators validate the data received and participate in further epidemiological studies.

Once causality is determined, the CSM generally uses the same mechanisms for dissemination of information as used in the United States: modifications of manufacturer's literature, "Dear Doctor" letters, publications from the CSM, and in worst cases compulsory withdrawal of the drug.^{8,13}

Attitudes

United States and United Kingdom. How is the relative success of these different systems affected by physician attitudes toward reporting? Inman described the "seven deadly sins" that inhibit reporting of ADRs in the United Kingdom: *complacency* about the safety of approved drugs, *fear* of litigation, *guilt* because of inadvertent harm caused to a patient, *ambition* to publish a personal series of cases, *ignorance* of reporting mechanisms, *diffidence* or reluctance in reporting mere suspicions, and *lethargy* resulting in an unwillingness to report these events.¹⁵ These seven characterizations were used as the basis for a small survey conducted at the Royal Liverpool Hospital to determine why physicians were reluctant to report ADRs.²

Sixty doctors were interviewed, about half of whom had reported ADRs, and a range of specialties was represented. The reasons these physicians gave for not reporting are reviewed in Table 2. Primarily, these physicians were diffident about reporting suspicions and ignorant of the reporting mechanisms.

The 1986 survey of Rhode Island physicians also explored possible reasons for physician underreporting of ADRs, albeit in different terminology. Physicians were questioned as to whether or not they were familiar with the FDA's voluntary reporting scheme and the forms and guidelines used by the FDA. They were then asked what factors would inhibit their use of it.

Table 2. Reasons Given by Physicians at the Royal Liverpool Hospital for Possible Hesitation in Reporting a Suspected ADR

Reason	%
Diffidence	39
Ignorance	37
Lethargy	13
Ambition	5
Complacency	2
Fear	2
Guilt	2

Of the 1,167 physicians who responded to the survey, 482 (41 per cent) reported they were unfamiliar with the FDA's reporting scheme; 661 physicians (57 per cent) were not familiar with the specific forms and guidelines. The reasons given by Rhode Island physicians for hesitating to report ADRs are reviewed in Table 3. Chief among those reasons is the perception that the forms were unavailable. In addition, physicians were uncertain about attributing the reaction to

Table 3. Reasons Given by Rhode Island Physicians for Possible Hesitation in Reporting a Suspected ADR to the FDA

Reason	No.	%*
Don't have forms	438	38
Couldn't be sure drug caused reaction	325	28
Reaction was expected	277	24
Don't know how	244	21
Reporting wouldn't occur to me	234	21
Concern over legal liability	88	8
Guidelines unclear	84	7
Don't have time	60	5
Forms too complex	40	3
Not my responsibility	7	<1

N = 1,167 (No information provided by 55 responders.)

* More than one response possible for each question.

a drug, and they believed the reaction was an expected one.

To compare the attitudes of the Rhode Island physicians with those of physicians at the Royal Liverpool Hospital, the reasons given by Rhode Island physicians for hesitating to report an ADR were classified where possible using Inman's terminology (Table 4). Consequently, "wouldn't occur to me" was identified as *complacency*, "don't have time" was classified as *lethargy*, "couldn't be sure drug caused reaction" matched *diffidence*, and "concern over legal liability" was the equivalent of *fear*. For our purposes, "ignorance" was determined by the earlier response to the question regarding physician familiarity with the FDA's forms and guidelines. Our survey did not query physicians about any guilt felt over iatrogenic harm or personal ambition to publish case reports.

Thus, physicians in Rhode Island (57 per cent) were more ignorant of the forms and guidelines

of the voluntary reporting system than were physicians in the Royal Liverpool Hospital (37 per cent). Rhode Island physicians were also much more likely to be complacent about the safety of drugs on the market and more concerned about malpractice litigation, although these numbers are small. On the other hand, physicians in the Liverpool hospital were more likely to be diffident about reporting their suspicions and less willing to exert themselves to report suspected ADRs (Table 4).

Source of Reports. The breakdown of sources of ADR reports received by the FDA and CSM may help in gaining insight into physician reporting behavior. In 1985 the FDA received 33,853 usable ADR reports from the following sources: manufacturer spontaneous reports (70 per cent), manufacturer foreign sources (14 per cent), health professionals (81 per cent), clinical studies (6 per cent), and reviews of the literature or reports from consumers (2 per cent).⁸ In contrast, in the years 1978 through 1982, the CSM received 78 per cent of its reports directly from physicians, 16 per cent from pharmaceutical companies, and 6 per cent from letters, including early reviews of manuscripts concomitantly submitted to medical journals.⁴

Consequently, the reporting behavior of British physicians suggests that they are more accustomed or willing to report suspected ADRs to the central regulatory body than are physicians in the United States. That the majority of physicians in the United Kingdom are associated with the National Health Service may help to explain this difference in reporting patterns. British physicians may simply be more inclined to deal directly with regulatory authorities.

A corollary of this behavior is that the Rhode Island Adverse Drug Reaction Project is discovering that physicians associated with health maintenance organizations are reporting ADRs at a higher rate than other groups. Approximately 15 per cent of total reports received by the project have been received from physicians at a pre-paid group practice, even though they constitute only about 5 per cent of physicians in the state.¹⁶

Spontaneous Reporting Systems: Summary

As here reported, postmarketing surveillance in the United States and the United Kingdom relies heavily on direct spontaneous reports from physicians, the crux of both systems. Spontaneous reporting has had both notable failures and successes. In the United States spontaneous reports revealed major drug safety problems following

Table 4. Comparison of Attitudes Toward Reporting Using Inman's Terminology: Rhode Island and Liverpool Physicians.

	Rhode Island %	Liverpool %
Ignorance	57*	37
Diffidence	28	39
Complacency	21	2
Fear	8	2
Lethargy	5	13

*Rhode Island physicians unfamiliar with the specific forms and guidelines used by the FDA.

use of zomepirac (Zomax[®]) and benoxaprofen (Oraflex[®]),¹⁷ while in the United Kingdom, the system first identified thromboembolic events associated with high doses of estrogen in oral contraceptives. However, the British yellow-card system was alarmingly slow in detecting any of the serious adverse effects (eg, sclerosing peritonitis) produced by practolol.¹⁴

These incidents illustrate both the benefits and disadvantages of voluntary reporting systems. The primary advantage is the virtually unlimited supply of sources for reports. In addition, spontaneous reporting systems are remarkably cost-effective. Rossi et al¹⁸ demonstrated that three Phase IV studies involving up to 22,653 patients revealed no ADRs not previously discovered through voluntary reporting systems.

Conversely, both postmarketing surveillance systems are plagued by gross underreporting, which makes a determination of true incidence impossible. Other disadvantages of voluntary reporting schemes are reporter bias and the desire of a physician unnecessarily to determine causality before filing a report.

The United States and the United Kingdom are dealing with the deficiencies of voluntary reporting systems differently. For example, in the United Kingdom a prescription-event monitoring scheme has been used by the Drug Surveillance Research Unit at Southampton University since 1980. The Prescription Pricing Authority identifies in confidence those patients who are receiving certain drugs to the Drug Surveillance Research Unit, which then surveys the prescribing doctors regarding their patients' experiences with the drug. Because this scheme enables the incidence of ADRs to be determined, prescription-event monitoring is rapidly becoming a second national postmarketing scheme.¹⁹

In the United States the FDA is attempting to modify the reporting behavior of physicians, in part by improving physician understanding of the vital importance of their individual reports. Consequently, the FDA has established pilot projects in five states, including Rhode Island, to study new interventions to stimulate more complete physician reporting. The Rhode Island project has tailored its interventions to changing the attitudes discovered in the survey that appear to impede reporting.

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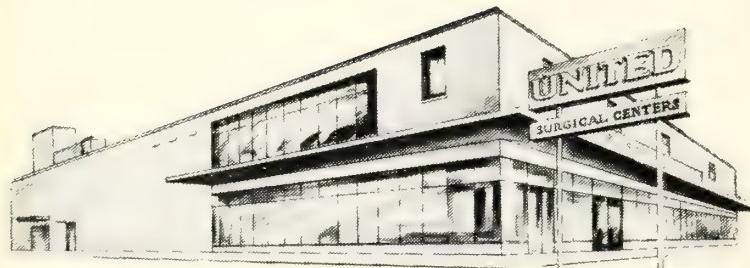
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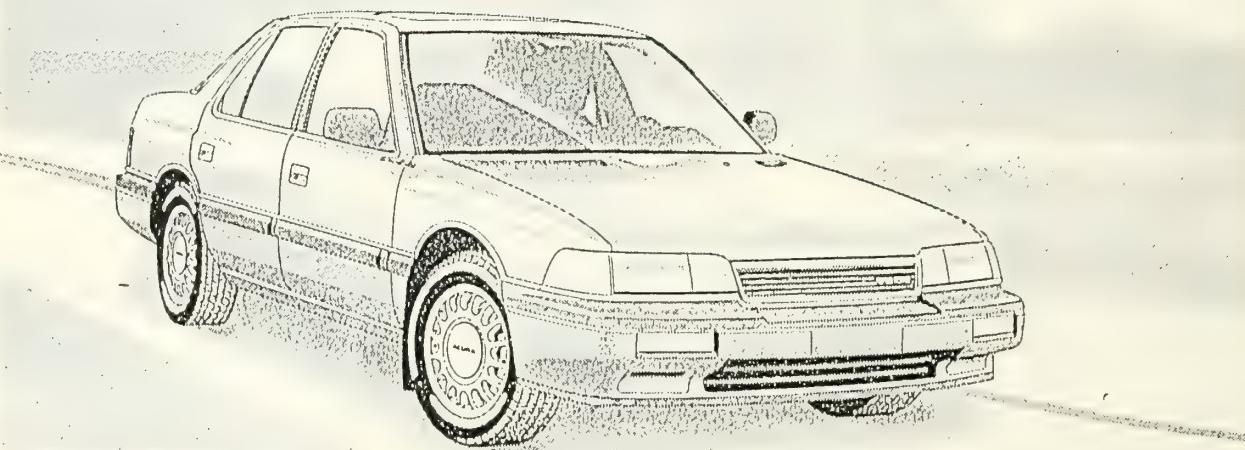
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Off-Site Day Care at The Institute of Mental Health 1982-1987

The Program Has Been Adversely Effected by Sacrificing Clinical in Favor of Administrative Goals

Nicholas Anez, BA

Historical Overview

The Rhode Island Medical Center, Institute of Mental Health (IMH), is the only public psychiatric hospital in the state. In the past several years, its patient population has been reduced from over 1300 to under 300. This was due in large part to the policy of "deinstitutionalization." Patients in need of varying degrees of supervision were placed in nursing or group homes, while others were released to their families or to independent living.

Wards and buildings were eventually closed, and the remaining population was divided into 2 groups: (1) *Acute Services*, which included new admissions, planning for whom was to return them to the community as soon as possible; (2) *Rehabilitative Services*, which included chronic patients who had been judged inappropriate for discharge. They had been hospitalized for 20 to 50 years and were regressed, dependent, in many cases assaultive, and displayed active symptoms of psychosis. Increased programming and more extensive documentation were deemed necessary for these patients. Since all types of treatment planning had thus far failed to achieve positive results, something entirely new would have to be attempted if the patient census was to be further reduced.

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Off-Site Day Care: Development and Implementation

In 1982 the most innovative program for the treatment of the chronic patients was formulated: the Off-Site Day Care Program. Developed by administrators of rehabilitative services who were members of the Psychology Department, this was a program in which patients and staff of a locked ward would be transported to a community setting three days a week for four hours a day. At these community "sites," the patients would be provided with activities and services which would not be possible in a hospital setting. The primary objective of the program was to reintroduce institutionalized patients into the community. It was theorized that new surroundings and familiar sights from pre-hospitalization lives would discourage dependency and reawaken long-dormant desires, interests, and emotions — and possibly decrease difficult behavior which may have been learned and conditioned by the institutional environment.

As part of the preparation for the program the administration enlisted the support of the treatment team members who worked with the patients on the wards and who would be attending the sites with the patients. The administrators emphasized that their desire was to work closely with the staff in all phases of planning and implementation. A coordinator was appointed who would serve as liaison between the staff and administration and who would travel with the patients daily. Responsibility was clearly divided.

All management decisions — such as choice of site, security at the sites, food for lunches, transportation and other non-clinical matters — were the responsibility of the administration. All clinical decisions — such as choosing the appropriate programming for each patient and deciding which patients might have to be omitted on a given day — was the responsibility of the staff. Since these were locked-ward patients, the nurse and attendants would decide daily if any of them should not attend. If negative behavior continued the treatment team would have the authority to remove them from the program for more appropriate on-ward activities. The team members who would be conducting group activities — psychiatrist, psychologist, activity therapist, and social worker — would have the authority to make all clinical decisions based upon their evaluation of each patient's needs. Since the staff members had other obligations, they had the option of returning to the hospital when their services were not required.

Four wards were chosen to initiate the program. The writer was assigned to two of these wards, one male and one female, each with 20 patients. This report will focus on these two wards. The average length of hospitalization for these patients was 27 years, and the average age was 54 years. Diagnoses were schizophrenia, chronic undifferentiated; organic brain syndromes (OBS) (two cases); and manic-depressive illness (one case). The two ward nurses and three attendants from each ward attended with the patients. The psychologist, the activity therapist, and the social worker, who were assigned to both wards, also attended. The psychiatrist, the team leader, attended one day a week. The central Providence YMCA in the heart of the city was selected as the site, a setting which the patients had not seen for decades.

The first few days were hectic. Some patients became belligerent and uncontrollable; some were frightened. Group meetings focused on discussing feelings. Recreational activities were provided to lessen anxiety. Selected patients were taken into the community to sit in a plaza, to walk the streets, and to view the sights.

Gradually, many patients began to adjust, particularly after the removal from the program of those who had been consistently disruptive and dangerous. Within three months, some stability had been achieved, and by six months the program had achieved a state of normality. Treatment included group meetings in community settings, recreational activities in the swimming pool

and gymnasium, and trips to restaurants, libraries, museums, and parks. Some patients, confined for years, were learning about life outside the institution. Some appeared to be developing motivation to leave the hospital. Others who had been socially isolated were displaying signs of interaction and increased awareness of their surroundings.

After one year the statistics were encouraging. Of 40 patients, 13 had been removed due to serious behavior problems (the manic-depressive patient was in this group). Of the remaining 27, 15 had thus far shown no change (including the two OBS patients). The remaining 12 had displayed some positive effects. None of these numbers remained constant. The condition of many patients fluctuated as they always had, regardless of circumstances, and some who had initially shown some interest became apathetic as the novelty wore off. But the number of patients who appeared to be steadily functioning at a higher level remained at about 10. Of this number, three were soon transferred to open wards, while two were processed for nursing home placement.

Other factors were relevant. One of the open ward candidates had twice previously been on an open ward, and one of the nursing home candidates had displayed interest since a companion had been placed. However, Off-Site was considered an essential factor in their improvement, although *how* essential was difficult to determine. In general, some tentative conclusions could be drawn. The patients with a history of violence showed the most opposition. Those who were severely regressed and uncommunicative remained as unresponsive to this program as to other programs. Those whose primary symptoms had been dependency and lack of motivation, but had previously enjoyed recreational trips and activities, showed the most improvement. The more elderly were less responsive and often became agitated during the afternoon when they were accustomed to taking a nap. Fluctuation was the norm for many. Finding a consistent factor in long-term improvement or regression was an elusive goal. Considering the type of patients involved, the program was considered to be successful by the end of its second year.

In 1984, the IMH proudly presented its reduced census, improved documentation, and — most prominently — the Off-Site Day Care Program to the Joint Commission on Accreditation of Hospitals (JCAH). It not only received accreditation, but was adjudged "the 2nd Best State Hospital in the Country."

Off-Site Day Care: 5 Years Later

As of December 1987, the IMH had further reduced its patient population to approximately 220. The two wards discussed in this report were closed, and the remaining patients (approximately 25, male and female) resided on a single ward until very recently, when it was gradually converted to an all-male ward. This was accomplished by transferring all the females to other wards and accepting males from other wards. These male patients shared at least one thing in common with the females who had left: they had all been consistently unresponsive to treatment planning and had remained severely psychotic. Since many of these patients had come from admission wards, the average age as well as the average length of hospitalization was lowered to some degree. The potential for assault, always a significant factor, increased. Two nurses and two attendants lost time at work due to injuries received from patients, while other patients are also frequently the victims of such assaults.

Despite the change in population, the day-care program has continued. One nurse, three attendants, the psychologist, the activity therapist, and the social worker continue to attend. The psychiatrist, traditionally the team leader, is no longer present. Shortly after the time-frame of this report, he was also assaulted by a patient and was out of work indefinitely. Many other changes in the program have evolved. The administration has assumed all authority, clinical and management. The staff is no longer involved in decision making. The site has changed several times and has included four churches in three cities, a mental health clinic, and at this writing a newly-remodeled building in affiliation with a community clinic. Programming at the site includes little that did not formerly occur at the hospital. Actual community penetration is minimal. In effect, the patients are transported from one closed setting to another closed setting.

Time spent at the site has been extended by one hour each day with proposed planning to extend the entire program by a fourth day. A typical day includes a community ward meeting followed by morning and afternoon groups. In between are two coffee breaks and the lunch hour which total 2 hours. The "social hour" concludes the day. Patients, when not agitated, spend a significant portion of the day sitting, smoking, drinking, waiting, and sleeping. Staff members no longer have the option of returning to the hospital when their services are not required.

Open-ward patients also now attend the site,

while clinic outpatients now attend under the policy of "Integration." It is theorized that chronic psychotic patients may learn more positive behavioral patterns if placed in close contact with outpatients.

Communication between the administration and the staff is now minimal. The administration views the program as beneficial and therapeutic to the patients. The staff views the program as consisting of a few benefits to the patients and more than a few detriments.

Specific Factors Directly Affecting the Program

Following the successful 1984 JCAH Accreditation, many IMH administrative personnel left the hospital for other positions. Personnel who replaced them, some new to IMH and some promoted from within, inherited a publicly successful hospital and were faced with the challenge of achieving further success. The new administration of the Off-Site Program included a social worker as assistant to a psychologist. The program — like its parent, IMH — also had to show continued progress which, as interpreted by administration, required an increase in the number of patients attending. This would mean — theoretically at least — that they were closer to discharge, thus complementing and achieving the hospital's goals, ie more programming, more discharges, and lower patient census.

However, the original patients who had improved had been transferred to open wards or discharged. They in turn had been replaced by patients whose level of functioning was similar to those who had thus far not shown any benefits. The more disruptive had been removed from the program, while the behavior of others fluctuated from day to day, resulting in as many as 12 patients being kept out on a given day. The administration felt that this was too high a number. When the staff would not reverse its decision, it assumed the clinical authority to decide who would attend. Patients from other wards as well as clinic outpatients were assigned to the program without consultation with the staff. Thus, the number of patients attending the program increased significantly.

Other clinical decisions were also assumed by the administration. Group leaders were told that they would have to expand their groups from 30 to 45 minutes, despite the difficulty of keeping chronic patients interested for even a half-hour. They were also told that they would have to accept patients from other wards as well as out-

patients into their groups, whether or not their needs were appropriate to the group's objectives and whether or not the group leader knew them or the specifics of their illnesses.

The administration's decision to extend the program sixty minutes each day for a "social hour" was also made without consulting the staff. Even prior to the time increase, staff members had been finding it increasingly difficult to complete other programming obligations. The staff also objected to the extra hour because of the belief that it would increase agitation in the more potentially violent patients who were now attending and would also increase stress among the more elderly. These fears were soon realized by an increase in behavioral incidents at the site.

Community penetration also decreased due to the lower level of functioning of the patients now attending. Contrary to theory, the behavior of these patients had shown no change at the site, and inappropriate and potentially dangerous behavior resulted in the elimination of activities away from the site for the majority of the patients. Thus, activities that formerly could occur only in the community were replaced by activities that could and formerly did take place at the hospital.

In times of inclement weather, on hot summer days or freezing winter days, the bus arrived on schedule, despite the staff's urgent request for cancellation. The administration paid for use of the site and would still have to pay for the day unless the clinic staff cancelled. At a meeting called by the IMH clinical administrator, the subject of Off-Site was raised, despite the fact that the purpose of the meeting was to expand other programming. One attendant, concerned about the effects of the freezing weather upon elderly patients, asked, "Would you want your mother to suffer like that?" There was no answer.

General Factors Indirectly Affecting the Program

At the IMH the negative effects of deinstitutionalization were gradually realized. Some patients in nursing homes were more restricted and confined than they had been at the hospital. Family members of patients who had been discharged in their care complained desperately of being unable properly to take care of their relatives and equally unable to arrange readmission due to the hospital's new strict admission policy. Increasing numbers of former patients who had been discharged to independent living were seen sleeping in alleys, begging food and handouts. Re-

ports of former patients committing crimes, being abused and exploited — and dying — occurred regularly. Yet the administration's policy of lowering the census had been achieved.

This policy of "Statistical Progress" appeared to filter down to the administration of the Off-Site Program. Increasing the number of patients attending, whether or not they were appropriate, reflected continued progress — on paper. The reality of the situation, as perceived by the staff who actually worked in the program appeared to be irrelevant. Many of these patients were incapable of receiving benefits from the program and were in need of alternative programming. Many too were as confined at the site as they would be at the hospital. Symptoms and anti-social behavior of many increased in severity. The stress upon the more elderly was unhealthy. The staff increasingly perceived the administration of both the IMH and of Off-Site to be primarily interested in maintaining the *appearance* of further progress rather than actual progress. Whether or not this perception was accurate the assumption of clinical authority by the administration and the resulting antagonism and lack of communication added to that perception.

Summary and Conclusions

For years the IMH had been viewed as a hopelessly overcrowded institution and an excessive drain upon the budget. Following the lead of other states, the IMH adopted the policy of deinstitutionalization and emptied buildings. However, as it became obvious that the number of psychiatric patients hadn't actually decreased but had been transported to the community, the policy soon became known as "dumping."

Theorizing that the inability of so many former patients to readjust to the community was due to inadequate preparation, the IMH again followed the lead of other states and developed the Off-Site Program, which achieved some initial success. But that success was selective and dependent upon many factors, some unidentifiable. In general, the largest percentage of success occurred during the initial stages of the program. As these patients were replaced by more difficult cases, there was a corresponding decrease in the incidence of improvement and a steady reduction in benefit to the patients. However, the fact that some patients had benefited was translated into the position that *all* patients would benefit, despite evidence to the contrary. The tentative conclusions that were available were ignored by the administration. Such conclusions were not

only imprecise, but were not measurable as well. Numbers and statistics on the other hand are measurable, and at the IMH the patient census became the measurable standard upon which success was defined. Similarly, in the Off-Site Program the number of patients attending became the measurable standard.

Adopting such standards prior to 1984 resulted in national recognition for the IMH; but "2nd Best" was not "No. 1." Thus, existing policies and programs, which contributed to such success, had to be continued and advanced if the IMH was to become "the Best State Hospital in the Country." The problems left by the previous administration — crowded admissions wards, community resentment to dumping, a remaining population that was inappropriate for discharge — could not be acknowledged if the census were to be further reduced. Similarly, the problems of Off-Site — the more receptive patients had benefited and left, while more regressed and difficult patients were attending — also had to be ignored if the number of patients attending were to increase.

In effect, the program's original objective of providing better patient care was discarded as perpetuation of the program itself became the objective. The necessity of advancing the program meant that evidence that it was not benefiting and indeed was anti-therapeutic to some patients could not be recognized. Opposition by the staff to the assignment of inappropriate patients to the program was resolved by taking away their clinical authority. Suggestions that the program had run its course were considered heresy. More moderate opinions that it should at least be streamlined to meet the requirements of selected patients based upon their clinical needs were equally disregarded.

If a program, especially one involving care of the mentally ill, is to have an opportunity to succeed, the direct care staff must be involved and motivated. Such support was carefully cultivated during the initial stages of the program, but discarded after initial success had been achieved. The breach between the staff and the administration was widened by policies which effected the staff's motivation and lowered its morale. Such policies would have been acceptable if they had resulted in better health care and a better quality of life for the patients. The absence of such benefits and increasing evidence of detrimental effects created an air of apathy and cynicism.

The IMH had placed the emphasis on discharge, while other needs of the patients were

lost in the process. Rather, they were reduced to being mere numbers. If deinstitutionalization had been applied in moderation and with selectivity, many of the failures could have been avoided. The Off-Site administration, adopting similar policies and objectives, placed the emphasis on the program and the patients were again reduced to mere statistics. The refusal to individualize patients, alienation of the staff and assumption of total authority assured ultimate failure of the program.

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INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFervescent POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemia/familial periodic paralysis.

2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: **Hyperkalemia**—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS**, **WARNINGS**, and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 ml.

3. Correction of acidosis, if present, with intravenous sodium bicarbonate.

4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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Political Action — The Example of BAYPAC

Involvement is Easy; Commitment is More Difficult

William E. Callahan, MD

Ten years ago, when I was becoming involved in medical politics on the state level, one of the first topics of interest for me was a discussion of the Bay State Physicians Political Action Committee (BAYPAC) which was to take place during the Massachusetts Medical Society (MMS) Council meeting. I mentioned this to my wife, who replied: "Sounds like a labor organization. That's not something doctors should be involved in. Politics are dirty and demeaning and not in the best interest of Medicine." The Massachusetts Council has 400 members, not like your concise organization. As the morning drew to a close, the president leaned over the podium and called, "O.K., Tom. You can have five minutes to discuss the PAC, but remember lunch is waiting." As the PAC chairman began to speak, two events occurred: one, the officers on the stage began talking with each other, ignoring the presentation, and two, the council members began filing out to get down to lunch! My wife was right! Politics did not belong in the camp of Medicine.

William E. Callahan, MD practices obstetrics in Greenfield, MA and is Chairman of the medical PAC of Massachusetts (BAYPAC).

Read at the RIMS House of Delegates meeting on January 28, 1988 at the Rhode Island Medical Society.

Five years later, when I was a member of the Legislative Committee of the MMS, we were embroiled in the Blue Cross-Blue Shield suit, (regarding the prohibition of balance billing), trying to wage a public relations campaign, having our brains beaten in on all of our legislative proposals and rapidly getting nowhere. The question asked of our lobbyists was WHY? The response was clear and concise: "It is said in the State House that if the MMS spent as much money on the Legislature as it has on the BS (Blue Shield) Suit, PR (public relations), etc. doctors would not be in the predicament that they currently found themselves." This was of course not the literal truth, but it did open up the eyes of many of us present. We found out that BAYPAC had only 22 members with a total bankroll of two thousand dollars, was operated out of an auxilian's home on a volunteer basis, and was floundering. At the same time, the legislative perception was that those FAT CATS won't spend a dime to help deserving legislators get re-elected, but have spent literally millions on lawyers and public relations. Is it any wonder that they were less than sympathetic to our problems?

It took an additional year-and-a-half to effect change in the PAC leadership and develop MMS headquarters support. Once we began to make some headway, we ran afoul of the Massachusetts Office of Campaign and Finance. The resulting flap almost soured the Society leadership on any

relationship with the PAC, but through education and communication we were able to find a common ground which would not cause either of us any discomfort and was not in violation of any arcane Massachusetts PAC laws. The specific issue that caused this turmoil was my exhortation to MMS members to contact their legislators and discuss the merits of two pieces of legislation. This is considered LOBBYING and as such is prohibited by LAW in Massachusetts.

I shall try to make clear what a PAC is, what it can do, and what it cannot do. I shall cover the relationship with AMPAC and its role (at least as it helped Massachusetts) and finally try to explain why a PAC, in spite of its limitations, is important in the entire political process.

What Is a PAC?

Quite simply, a PAC is a group of individuals who have come together for the purpose of electing or re-electing candidates for the Legislature who they believe will be favorably disposed to their views on matters of interest to Medicine. This is a nation of associations or PACS. Jefferson felt that only by having competing interests represented could a balance be brought to bear and a consensus reached which would be good for all the people.

What Does a PAC Do?

A PAC evaluates the voting record of a legislator, or the speeches of a candidate, interviews the candidate to verify access, intent, and consistency with the PAC's goals, educates its contributors about the issues, and contributes to the candidates election/re-election campaign.

What Does a PAC Not Do?

The PAC does not lobby. It does not make a contribution based on the promise of a vote for or against an issue. It is obvious that when you discuss legislation with a legislator you are lobbying. In Massachusetts when you discuss legislative issues with anyone you may be indirectly lobbying. Indirect lobbying by a PAC is also prohibited in Massachusetts. The main message here is RESEARCH and know your PAC laws!!

Relationship With AMPAC

AMPAC is extremely helpful in coordinating mailings, follow-up solicitations, and upgrade requests. They sponsor a Political Education Seminar, a Campaign Managers School, and a How To Be A Candidate Seminar. With your approval and recommendation, AMPAC will support your

congressmen — senators and representatives — for up to \$10,000 for the primary and general election. AMPAC relies on your information as well as the access the AMA lobbyists have and your congressman's voting records to determine support levels.

Twenty dollars of your regular membership and \$50 of a sustaining membership is sent to AMPAC. Generally speaking, AMPAC will spend more for Rhode Island than it receives from you.

AMPAC does not support either presidential candidate. It is a good rule for state PACS not to support statewide office holders either.

Why Is a PAC Important?

This can be summed up in three words — *Unity, Voting Power, and Money*. Elected officials view groups of people with more caution and respect than individuals. A PAC indicates common purpose, resolve, and influence upon your representative. The PAC is felt to be able to mobilize blocks of voters on a given issue or candidate. In politics perception is reality! Imagine the thought of 1000 offices statewide discussing political issues with 20 or 30 people a day! Finally, your ability to raise and distribute contributions indicates the amount of power you have at your disposal. These elements — votes, money and power — are more persuasive in many instances than truth and knowledge when dealing with legislators.

How Do You Resolve the Issue of Party?

I have found that labels are meaningless when it comes to political issues and support. In Massachusetts, a one-party state for all intents and purposes, the Democratic Party encompasses the whole range of political views — from frankly and openly Socialistic/Communistic to ultra-Liberal. So that party labels are meaningless. Similarly, one man's conservative is another's liberal. For example, I consider myself a Pragmatic Idealist; my wife calls me a Rank Opportunist.

Look at voting records on medical issues, position in the power hierarchy, how much harm can he do if ignored, and finally will your support change his perception of the issues so that the PAC can make a valid decision regarding contributions. Beyond contributions, individuals become an integral part of the political apparatus of the legislator of your choice or the party of choice. In the long run, this will be even more beneficial as long as the PAC support is in place.

The *Key to Success* for the PAC is *Involvement*; for Medicine it is *Commitment*. Involvement is easy-

write out a check; make a few phone calls. Commitment is much more difficult. I don't have a set example of what commitment is or should be, but let me close with a concrete example of the difference.

This morning when my breakfast plate was placed before me with its two eggs staring up at me and a rasher of bacon, I thought "The hen that produced those eggs was certainly involved in my breakfast, but the pig — That's *Commitment!*"

Received for publication February 1, 1988

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PERIPATETICS

The American Association for Hand Surgery recently elected **Dr Lee Edstrom**, Rhode Island Hospital, Division of Plastic Surgery, as its President at the annual meeting in Puerto Rico.

• • •

Dr John J. Cunningham, Associate Chairman, Family Medicine at The Memorial Hospital in Pawtucket and **Dr David S. Greer**, Family Medicine and Dean of Medicine at Brown University, have been appointed to two-year terms as American Medical Association representatives on the Residency Review Committee for Family Practice.

• • •

The National Nominating Committee of the Triological Society (the American Laryngological, Rhinological, and Otological Society) has recently elected **Dr Mary D. Lekas**, Surgeon-in-Chief, Department of Otolaryngology and Chairman at Brown University, to membership. The Triological Society, requiring a thesis for membership, is the most prestigious society in the specialty of Otolaryngology. **Dr Lekas** is also the RI delegate on the Board of Governors of the American Academy of Otolaryngology — Head and Neck Surgery.

• • •

Dr Dennis S. Krauss, in the Endocrinology Division at The Memorial Hospital in Pawtucket, has recently been elected president of the Diabetes and Endocrine Society of Rhode Island, as well as being named to fellowship in the American College of Physicians.

• • •

The American Psychiatric Association has elected **Dr Richard J. Goldberg**, chief of the Department of Psychiatry, Rhode Island Hospital, as a fellow.

• • •

Recipient of the 1987-88 Melvin D. Hoffman Scholar Award is **Dr William J. Kassler**, senior medical resident at Rhode Island Hospital. **Dr Kassler** is the first recipient of the award, named in honor of Dr Hoffman, a medical staff member at Rhode Island Hospital from 1957-1984. Each year the award will be presented to a member of the General Internal Medicine Residency Program, to assist in the undertaking of a project or program of learning.

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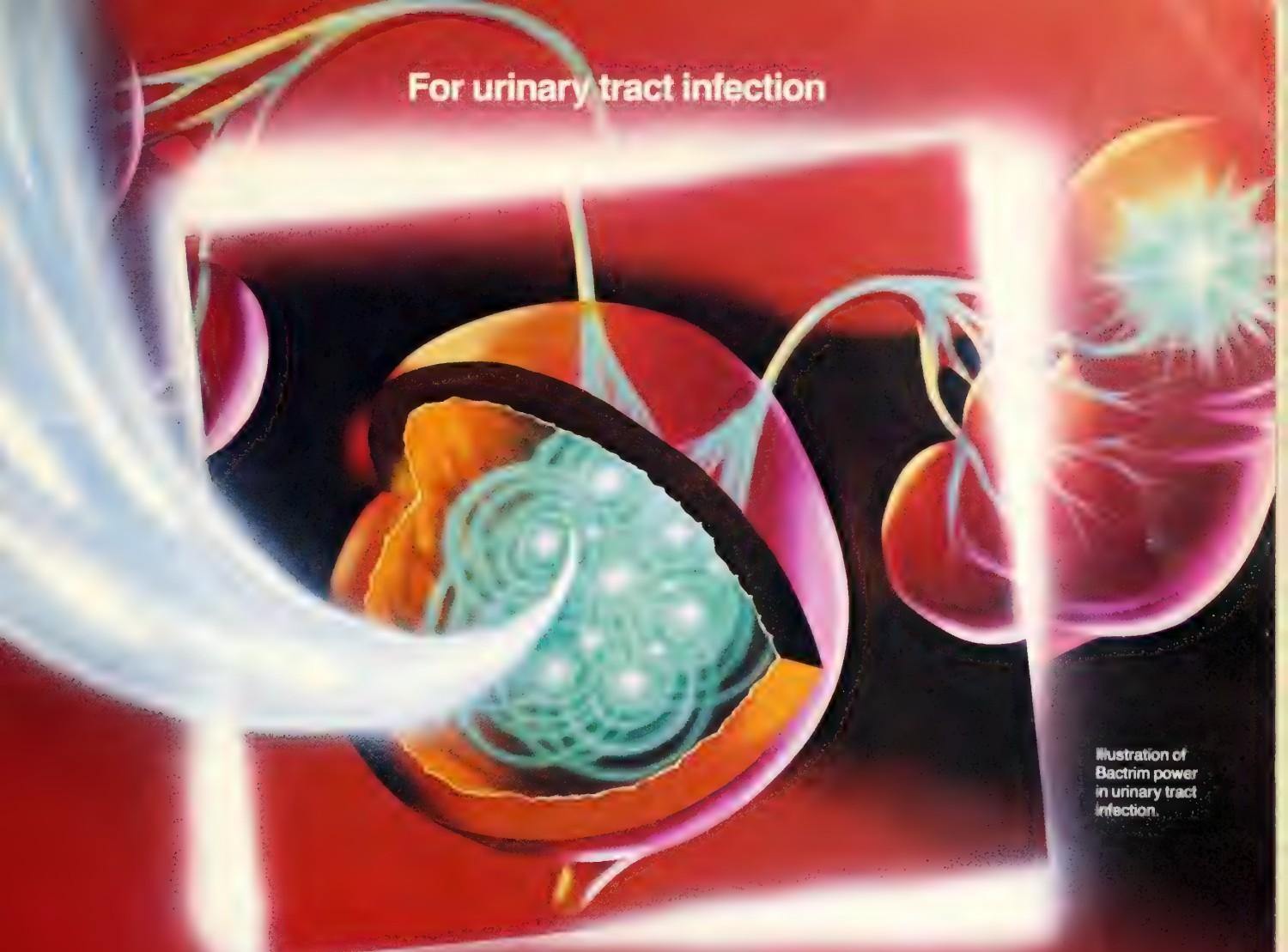
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Bactrim™ DS

(160 mg trimethoprim and 800 mg sulfamethoxazole/Roche)

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Please see references and summary of product information on following page.



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Bactrim™

(trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides, documented megaloblastic anemia due to folate deficiency, pregnancy at term and during the nursing period; infants less than two months of age.

WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS

BACTRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice, may be early indications of serious reactions. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Perform complete blood counts frequently.

BACTRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Bactrim than with penicillin.

PRECAUTIONS: General: Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (e.g., elderly, chronic alcoholics, patients on anticonvulsants, with malabsorption syndrome, or in malnutrition states) and severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur, frequently dose-related.

Use in the Elderly: May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, e.g., impaired kidney and/or liver function, concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly. In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura reported. Make appropriate dosage adjustments for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION).

Use in the Treatment of *Pneumocystis Carinii* Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS): AIDS patients may not tolerate or respond to Bactrim in same manner as non-AIDS patients. Incidence of side effects, particularly rash, fever, leukopenia, elevated aminotransferase (transaminase) values, with Bactrim in AIDS patients treated for *Pneumocystis carinii* pneumonia reported to be greatly increased compared with incidence normally associated with Bactrim in non-AIDS patients.

Information for Patients: Instruct patients to maintain adequate fluid intake to prevent crystalluria and stone formation.

Laboratory Tests: Perform complete blood counts frequently. If a significant reduction in the count of any formed blood element is noted, discontinue Bactrim. Perform urinalyses with careful microscopic examination and renal function tests during therapy, particularly for patients with impaired renal function.

Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. Keep this in mind when Bactrim is given to patients already on anticoagulant therapy and reassess coagulation time. Bactrim may inhibit the hepatic metabolism of phenytoin. Given at a common clinical dosage, it increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When giving these drugs concurrently, be alert for possible excessive phenytoin effect. Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

Drug Laboratory Test Interactions: Bactrim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs if methotrexate is measured by a radioimmunoassay (RIA). The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffe alkaline phosphatase reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis. Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim. Mutagenesis: Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination. Concentrations used exceeded blood levels of these compounds following therapy with Bactrim. Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities. Impairment of Fertility: No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

Pregnancy Teratogenic Effects: Pregnancy Category C. Trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefit justifies potential risk to fetus. Nonteratogenic Effects: See CONTRAINDICATIONS section.

Nursing Mothers: See CONTRAINDICATIONS section.

Pediatric Use: Not recommended for infants under two months (see INDICATIONS and CONTRAINDICATIONS sections).

ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION)** Hematology: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia. Allergic Reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schönlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. Periorbital nodosa and systemic lupus erythematosus have been reported. Gastrointestinal: Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia. Gastrointestinal: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystaluria. Neurologic: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. Psychiatric: Hallucinations, depression, apathy, nervousness. Endocrine: Sulfonamides bear certain chemical similarities to some goitrogenic diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, cross-sensitivity may exist. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Respiratory: Pulmonary infiltrates. Musculoskeletal: Arthralgia, myalgia. Miscellaneous: Weakness, fatigue, insomnia.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN: Usual adult dosage for urinary tract infections is one DS tablet, two tablets or four teaspoonsful (20 ml) b.i.d. for 10 to 14 days. Usual identical daily dosage for 5 days for shigellosis. Recommended dosage for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses every 12 hours for 10 days. Use identical daily dosage for 5 days for shigellosis. Renal Impaired: Creatinine clearance above 30 ml/min, give usual dosage. 15-30 ml/min, give one-half the usual regimen, below 15 ml/min, use not recommended.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS: Usual adult dosage is one DS tablet, two tablets or four teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONIA: Recommended dosage is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

HOW SUPPLIED: DS (double strength) Tablets (160 mg trimethoprim and 800 mg sulfamethoxazole)—bottles of 100, 250 and 500, Tel-E-Dose® packages of 100. Prescription Paks of 20 Tablets (80 mg trimethoprim and 400 mg sulfamethoxazole)—bottles of 100 and 500, Tel-E-Dose® packages of 100. Prescription Paks of 40. Pediatric Suspension (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 100 ml and 16 oz (1 pint). Suspension (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 16 oz (1 pint).

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HAVE YOU HEARD?

A report in the March *Archives of Neurology* states that some drugs used to treat parkinsonism may mimic or exacerbate the clinical signs of Alzheimer's disease. A 74-year-old parkinsonian patient who developed progressive cognitive and behavioral problems suggesting Alzheimer's disease is described by Roger Kurlan, MD, and Peter Como, PhD of the University of Rochester, (NY) School of Medicine. These disturbances were reversed after the patient was taken off his anti-parkinsonism medication — an anticholinergic agent, which works to block a neurotransmitter believed involved in parkinsonian symptoms. "The appearance of cognitive decline in patients with parkinsonism may not necessarily be caused by progressive degenerative processes, and withdrawal of anticholinergic medications should be considered for all parkinsonian patients who develop cognitive or behavioral disturbances," the authors say.

• • •

Patients spending a minimum of two nights in a sleep laboratory to be evaluated for chronic insomnia showed differing results from assessments based on interviews in 49 per cent of the cases. In the March issue of the *American Journal of Psychiatry*, a research team from Western Psychiatric Institute and Clinic and the University of Pittsburgh School of Medicine say these differences resulted in substantial changes in the initial findings and then a more specific diagnosis. The sleep-related disorders were diagnosed by polysomnography, the all-night recording of a variety of parameters, such as brain waves, eye movements and heart rate. The team stated that polysomnography would be helpful for patients with insomnia who have been treatment resistant — not responding to regular clinical interventions. They stress that they are not suggesting that the procedures should "replace the clinician's acumen."

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Patients infected with the AIDS virus but not yet seriously ill are being offered Retrovir (zidovudine) treatments by researchers at five Veterans Administration Medical Centers — in San Francisco, Miami, Houston, Los Angeles, and Manhattan. Over 400 seropositive patients whose CD4 lymphocyte counts are lower than normal — but not as low as those of patients with AIDS or ARC — will be treated over the next four years. The health of the study patients will be monitored, with extensive laboratory studies possibly providing researchers with a scale on which to weigh Retrovir's toxicity against potential benefits.

• • •

The Harvard Medical School recently conducted research that concludes aspartame (Nutrasweet) can help people lose weight and does not increase appetite. This report appeared in a recent issue of *Calorie Control Commentary*. Dr George Blackburn, who headed the Harvard research team, stated that the "study indicates that aspartame is a valuable adjunct to a comprehensive program of balanced diet, exercise, and behavior modification for losing weight." Fifty-nine obese men and women on calorie-restricted diets were involved in the twelve-week pilot study. The control group had instructions not to consume aspartame products while some of the subjects were encouraged to snack on products containing aspartame. Weight loss as well as measures of general well-being (hunger, craving for sweets, energy levels) were compared in the study. Those of the 46 women in the study who consumed the aspartame-containing products lost an average of 16.5 pounds, about four pounds more than the control group. Male users of aspartame lost slightly less weight but these results were inconclusive in relation to the number of male participants (13). Consumers of aspartame also showed "favorable responses, i.e., perceptions of increased energy level, well-being, and activity level."

YOCON® YOHIMBINE HCI

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. MacMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85



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Before prescribing, see complete prescribing information in SK&F LAB CO. literature or PDR. The following is a brief summary.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: While a weak antidiuretic effect has been demonstrated in animals, 'Tagamet' has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity in humans.

In a 24-month toxicity study in rats at dose levels approximately 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'.

Rare instances of cardiac arrhythmias and hypertension have been reported following the rapid administration of 'Tagamet' HCl (brand of cimetidine hydrochloride) injection by intravenous bolus.

Symptomatic response to 'Tagamet' therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states have been reported on occasion, predominantly in severely ill patients.

'Tagamet' has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlordiazepoxide, diazepam, lidocaine, theophylline and metronidazole. Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when 'Tagamet' is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either 'Tagamet' 300 mg. q.i.d. or 800 mg. h.s. concomitantly with a 300 mg. b.i.d. dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc.),

demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg. h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. [Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.]

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of childbearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should not be undertaken in patients taking the drug since cimetidine is secreted in human milk.

Adverse Reactions: Diarrhea, dizziness, somnolence, headache, rash. Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported. Reversible confusional states (e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported. Gynecomastia and reversible impotence in patients with pathological hypersecretory disorders receiving 'Tagamet', particularly in high doses, for at least 12 months, have been reported. Reversible alopecia has been reported very rarely. Decreased white blood cell counts in 'Tagamet'-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and a few cases of aplastic anemia have also been reported. Increased serum transaminase and creatinine, as well as rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including hypersensitivity vasculitis, have been reported. Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly un-

likely. A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving 'Tagamet' has been reported.

How Supplied: Tablets: 200 mg. tablets in bottles of 100; 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 [Intended for institutional use only]; 400 mg. tablets in bottles of 60 and Single Unit Packages of 100 [Intended for institutional use only], and 800 mg. Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 [Intended for institutional use only].

Liquid: 300 mg./5 ml., in 8 fl. oz. (237 ml.) amber glass bottles and in single-dose units (300 mg./5 ml.), in packages of 10 [Intended for institutional use only].

Injection:

Vials: 300 mg./2 ml. in single-dose vials, in packages of 10 and 30, and in 8 ml. multiple-dose vials, in packages of 10 and 25.

Prefilled Syringes: 300 mg./2 ml. in single-dose pre-filled disposable syringes.

Plastic Containers: 300 mg. in 50 ml. of 0.9% Sodium Chloride in single-dose plastic containers, in packages of 4 units. No preservative has been added.

ADD-Vantage® Vials: 300 mg./2 ml. in single-dose ADD-Vantage® Vials, in packages of 25.

Exposure of the premixed product to excessive heat should be avoided. It is recommended the product be stored at controlled room temperature. Brief exposure up to 40°C does not adversely affect the premixed product.

'Tagamet' HCl (brand of cimetidine hydrochloride) injection premixed in single-dose plastic containers is manufactured for SK&F Lab Co. by Travenol Laboratories, Inc., Deerfield, IL 60015.

* ADD-Vantage® is a trademark of Abbott Laboratories.

BRS-TG-L73B

Date of issuance Apr. 1987

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brand of cimetidine
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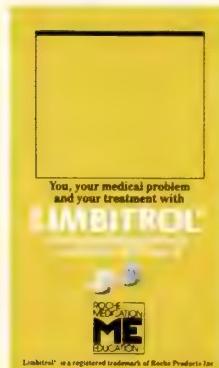
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This important program helps your patients remember and understand:

- What the medication is and why they are taking it
- The importance of staying with the prescribed course of treatment
- What foods and drinks to avoid
- Possible side effects

For a free supply of Limbitrol booklets, complete the coupon below and mail it to: Professional Services Department, Roche Laboratories, a division of Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, New Jersey 07110-1199

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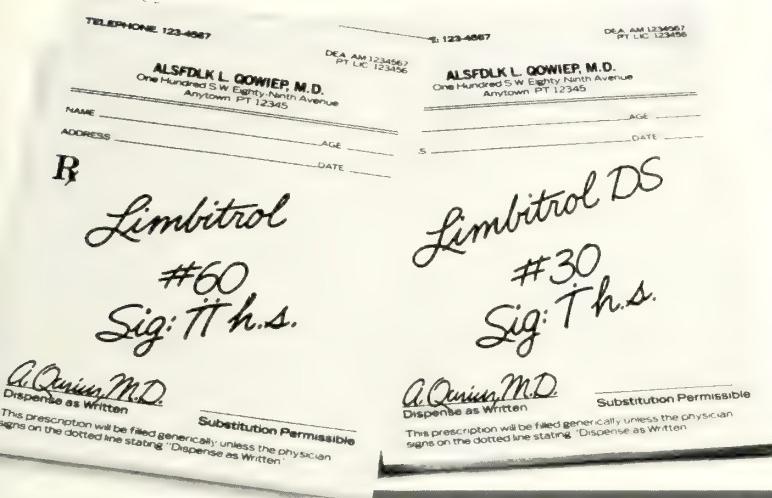
PLANDEX 35201

In moderate depression and anxiety

→ 74% of patients experienced improved sleep after the first h.s. dose¹

→ First-week improvement in somatic symptoms¹

→ 50% greater improvement with Limbitrol in the first week than with amitriptyline alone²



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Specify "Do not substitute."

Limbital®

Each tablet contains 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt) **IV**

Limbital DS®

Each tablet contains 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) **IV**

References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Feighner VP, et al: Psychopharmacology 61:217-225, Mar 22, 1979.

Limbital® **IV**

Tranquilizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants; concomitant use with MAOIs or within 14 days of monoamine oxidase inhibitors (then initiate cautiously, gradually increasing dosage until optimal response is achieved); during acute recovery phase following myocardial infarction.

Warnings: Use with caution in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur when used with anticholinergics. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia, prolongation of conduction time, myocardial infarction and stroke reported with tricyclic antidepressants, especially in high doses. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester

should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs. **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. **Neurologic:** Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extra-pyramidal symptoms, syncope, changes in EEG patterns. **Anticholinergic:** Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. **Allergic:** Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus. **Hematologic:** Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. **Endocrine:** Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Overdosage: Immediately hospitalize patient. Treat symptomatically and supportively. I.V. administration of 1 to 3 mg physostigmine salicylate may reverse symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

How Supplied: Double strength (DS) Tablets, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and Tablets, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.



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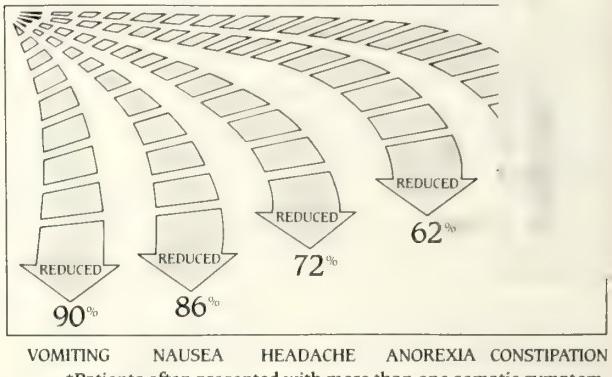
In the depressed and anxious patient

See Improvement In The First Week And The Weeks That Follow

- 74% of patients experienced improved sleep after the first *h.s.* dose¹
- First-week reduction in somatic symptoms

Caution patients about the combined effects of Limbitrol with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car. In general, limit dosage to the lowest effective amount in elderly patients.

Percentage of Reduction in Individual Somatic During First Week of Limbitrol Therapy



*Patients often presented with more than one somatic symptom.

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Each tablet contains 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt) IV

Limbital DS®

Each tablet contains 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) IV

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Please see summary of product information inside back cover.



RHODE ISLAND MEDICAL JOURNAL



June 1988

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A LOOK AT THE NURSING PROFESSION

(See page 229)

Thalidomide and D.E.S. (They could happen again.)

Sometimes even the most promising drug may have unexpectedly adverse reactions in patients. Pre-market testing identifies most toxic drugs before release for patient-care use, but not all. Toxicity in some drugs can only be determined through adverse reactions detected among a larger number of patients over a longer period of time.

The plain truth is that a patient's health may be at risk. Adverse drug reactions cause death in approximately 30,000 patients annually in the United States alone. So, if you suspect an adverse drug reaction, please report it promptly. We may all live longer because you did.



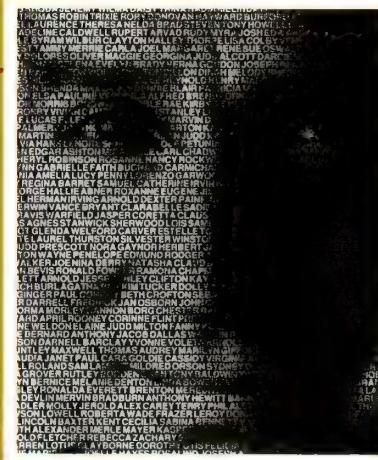
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of the Rhode Island Department of Health

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Like conventional INDERAL Tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree and bronchial asthma.

ONCE-DAILY
INDERAL® LA
(PROPRANOLOL HCI)
LONG ACTING
CAPSULES
60, 80, 120, 160 mg

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Please see next page for brief summary of prescribing information.

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(PROPRANOLOL HCl)
LONG ACTING CAPSULES
60, 80, 120, 160 mg

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60 mg 80 mg 120 mg 160 mg

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® LA brand of propranolol hydrochloride (Long Acting Capsules)

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. Inderal is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by Inderal, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Inderal LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with Inderal LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of Inderal Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

Inderal LA should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to Inderal LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, Inderal LA has been therapeutically equivalent to the same mg dose of conventional Inderal as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. Inderal LA can provide effective beta blockade for a 24-hour period.

INDICATIONS AND USAGE. **Hypertension:** Inderal LA is indicated in the management of hypertension; may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. Inderal LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: Inderal LA is indicated for the long-term management of patients with angina pectoris.

Migraine: Inderal LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: Inderal LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. Inderal LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. Inderal is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with Inderal.

WARNINGS. **CARDIAC FAILURE:** Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitized and/or treated with diuretics, and the response observed closely, or Inderal should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of Inderal therapy. Therefore, when discontinuance of Inderal is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If Inderal therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute Inderal therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Inderal should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Inderal (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta blockers should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid function tests, increasing T₄ and reverse T₃, and decreasing T₃.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Propranolol should be used with caution in patients with impaired hepatic or renal function. Inderal (propranolol HCl) is not indicated for the treatment of hypertension.

Beta-adrenoceptor blockade can cause reduction of intraocular pressure. Patients should be told that Inderal may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if Inderal (propranolol HCl) is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbital, and rifampin accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and lidocaine have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T₃ concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

PREGNANCY: Pregnancy Category C. Inderal has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. Inderal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: Inderal is excreted in human milk. Caution should be exercised when Inderal is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of propranolol.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasisiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctiva reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. Inderal LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from Inderal Tablets to Inderal LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. Inderal LA should not be considered a simple mg-for-mg substitute for Inderal. Inderal LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION — Dosage must be individualized. The usual initial dosage is 80 mg Inderal LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypotensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS — Dosage must be individualized. Starting with 80 mg Inderal LA once daily, dosage should be gradually increased at three- to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE — Dosage must be individualized. The initial oral dose is 80 mg Inderal LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, Inderal LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS — 80-160 mg Inderal LA once daily.

PEDIATRIC DOSAGE — At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Reference:

1. Data on file, Ayerst Laboratories.

D7295/188



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A REVOLUTIONARY ORAL ANTIMICROBIAL WITH THE POWER OF PARENTERALS

- Highly active *in vitro* against a broad range of gram-positive and gram-negative pathogens, including methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa**
- For treatment of infections in the:
 - lower respiratory tract†
 - skin/skin structure†
 - urinary tract†
 - bones and joints†
- Convenient *B.I.D.* dosage – 250 mg, 500 mg and 750 mg tablets

**In vitro* activity does not necessarily imply a correlation with *in vivo* results.

†Due to susceptible strains of indicated pathogens. See indicated organisms in Brief Summary.

CIPRO® SHOULD NOT BE USED IN CHILDREN OR PREGNANT WOMEN.

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.



Miles Inc.
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

Please see adjacent page of this advertisement for Brief Summary of Prescribing Information.

Cipro® TABLETS

(ciprofloxacin HCl/Miles)

**500 mg B.I.D. for most infections;
750 mg B.I.D. for severe or complicated infections.**

BRIEF SUMMARY

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION INDICATIONS AND USAGE

Cipro® is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Lower Respiratory Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Pseudomonas mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae*.

Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Pseudomonas mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (penicillinase and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, and *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Pseudomonas mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri*, and *Shigella sonnei** when antibacterial therapy is indicated.

Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with Cipro® may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINdications

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN OR PREGNANT WOMEN. The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and very rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals. Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded. Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

Drug Interactions Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired, concurrent administration of these agents with ciprofloxacin should be avoided.

Probencid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum concomitantly or within two hours after dosing. Ciprofloxacin may cause dizziness or lightheadedness, therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Carcinogenesis, Mutagenesis, Impairment of Fertility *In vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below.

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V₇₉ Cell HGPT Test (Negative)

Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the following three *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in animals have not yet been completed.

Pregnancy – Pregnancy Category C Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in

CONVENIENT B.I.D. DOSAGE

Recommended dosage schedule

Infection Site*	Severity of Infection	Dosage
Respiratory Tract*	Mild/Moderate	500 mg B.I.D.
Bone and Joint*	Severe/Complicated	750 mg B.I.D.
Urinary Tract*	Mild/Moderate	250 mg B.I.D.
	Severe/Complicated	500 mg B.I.D.
Infectious Diarrhea*	Mild/Moderate/Severe	500 mg B.I.D.

pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers

It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this, and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Ciprofloxacin should not be used in children because it causes arthropathy in immature animals (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, primarily related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%).

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below. Those typical of quinolones are italicized.

GASTROINTESTINAL (See above), painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM (See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.

SKIN/HYPERSensitivity (See above), pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctiva or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

SPECIAL SENSES blurred vision, disturbed vision, (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, bad taste.

MUSCULOSKELETAL joint or back pain, joint stiffness, aching, neck or chest pain, flare-up of gout.

RENAL/UROGENITAL interstitial nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY epistaxis, laryngeal or pulmonary edema, hiccup, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Adverse Laboratory Changes Changes in laboratory parameters listed as adverse events without regard to drug relationship.

Hepatic – Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Hematologic – eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal – Elevations of Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED

Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukodystrophy.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. In the event of serious toxic reactions from overdosage, hemodialysis or peritoneal dialysis may aid in the removal of ciprofloxacin from the body, particularly if renal function is compromised.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro® (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE INFORMATION).

* Due to susceptible strains of indicated pathogens. See indicated organisms in Brief Summary.

**For further information, contact the Miles Information Service:
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Cover: Photograph of a nurse, circa 1900, courtesy of the Rhode Island Historical Society.

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The Trustees of the Caleb Fiske Fund invite readers of the RHODE ISLAND MEDICAL JOURNAL to submit nominations for the 1988 Fiske Prize Competition for scholarly writing in medicine.

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EDITORIAL

RIMS-IBC: The Rhode Island Medical Society Insurance Brokerage Corporation

Some years ago when Erminio Cardi was treasurer of the Society, he noted that, when a member purchased malpractice insurance from the Rhode Island Joint Underwriters Association (RIJUA), he or she was obliged to do so through an existing insurance broker or agency. The broker retained the automatic sales commission, for which it provided almost no visible service. Cardi urged that the Society form its own captive agency, thus profiting from the sale of each policy. There were administrative hurdles to implementing such a project, and skeptics prevailed in deferring the plan.

Good ideas, however, have a way of coming to fruition in the end. In early March of this year RIMS finally activated its wholly-owned subsidiary, the RIMS Insurance Brokerage Corporation, chartered as a for-profit corporation. Its purpose is to serve *all* health-care providers who buy their liability insurance from the RIJUA — physicians, dentists, osteopathic physicians, nurses, podiatrists, laboratories, technologists, hospitals, and nursing homes. It offers only professional liability insurance written by the local JUA.

Activation of the IBC is another of the Society's manifold endeavors to serve its members and thus their patients. It is also in keeping with current trends of professional associations to augment their often over-committed income from non-dues sources. The American Medical Association, for example, derives less than one-half of its income from members' dues.

The Board of Directors of the IBC is elected by the Council of the Society. The present incumbents are: Paul J.M. Healey, chairman; Boyd P. King, vice chairman; Richard Bertini; Robert O'Neill; and Richard M. Divver. Here are several questions which may come to mind and their answers:

Will I pay less for my medical liability insurance?
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Why should I purchase my JUA Policy through RIMS-IBC?

There are two basic reasons. First, you will receive quality service. Drawing on twelve years' experience in medical liability underwriting in Rhode Island, our professional staff is uniquely qualified to give you prompt, knowledgeable attention.

Second, you will be helping to create a better climate for medicine and health care in Rhode Island. Among other things, profits of the IBC may be used to promote tort reform, support efforts to reduce malpractice insurance premiums, and to complement other efforts and programs of the Rhode Island Medical Society.

What do I need to do to apply?

Call the IBC at (401)272-1050 and make the RIMS-IBC your agent of record for medical liability insurance. You will be sent a simple form to fill out and return. The IBC can then be in touch with you automatically when your next policy renewal comes due.

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Seebert J. Goldowsky, MD

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The Impending Crisis at the Bedside

With an increasing number of women entering the work force, it is obvious that these women are not choosing nursing as a career. The once glamorous image of Florence Nightingale has now dimmed considerably. The personal fulfillment gained from caring for a patient is now greatly offset by negative factors which include low salary, lack of recognition, stress, burn-out, and odd work hours. The bedside role is being abandoned in favor of other more prestigious careers in the health-care field such as administration or further education to become a physician.

Hospitals across the country are now taking steps to encourage more women to opt for nursing as a profession. In Rhode Island, where there is a marked decrease in graduates from nursing schools, legislation is in the making to establish a loan program for student nurses.¹ The program would allow a student to borrow \$1,000 a year for four years. For each year the graduate is employed as a nurse in Rhode Island, a year of loan payments would be deducted.

Nurses complain that they are not perceived as valuable contributors to patient care. A more active role in decision-making will help dispel the notion that being a nurse lacks status and thus will improve self esteem. As is occurring in other endeavors, the provision of day-care in hospital settings is another device for attracting nurses. Recognizing that many nurses have a parental role to play as well engenders greater respect between nurse and employer and is also a means of relieving added stress.

There is evidence in the classified section of the *Providence Journal-Bulletin* that attempts are being made to improve the image of nurses. Emphasis on the value of patient care, advancement opportunities, and personal recognition is prominent among the various hospital job descriptions. The competition in salaries is also clear from the advertisements—an immediate answer to the growing shortage of nurses. An example of this trend is the substantial increase in salaries recently granted to nurses at Butler Hospital. Though hospitals are currently concerned with the necessity of cost-cutting measures, the salaries of nurses are not an appropriate place for economy. After all, the nursing staff is crucial to

the smooth running of the hospital. Providing a poor quality of nursing care is certainly not cost-effective. While the amenities add to the attractiveness of a nursing career, the critical factor is salary.

Kimberly J. Allyn

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2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for uroribinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions—No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenesis study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high dose males compared to placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement.

compared to concurrent controls, and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive, and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery is not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, and the mouse lymphoma assay.

In a two-generation, perinatal and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose, and in Dutch Belted rabbits at doses up to 55 times the human dose, revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White Rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Nizatidine is secreted and concentrated in the milk of lactating rats. Pups reared by treated lactating rats had depressed growth rates. Although no studies have been conducted in lactating women, nizatidine is assumed to be secreted in human milk, and caution should be exercised when nizatidine is administered to nursing mothers.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among the more common adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported, it was not possible to

determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antidiuretic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic—Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H₂-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients. Rash and exfoliative dermatitis were also reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported.

Overdosage: There is little clinical experience with overdosage of Axid in humans. If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous LD₅₀ values in the rat and mouse were 301 mg/kg and 232 mg/kg respectively. PV 2091 AMP [041288]

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Initial Experience with Extracorporeal Shock Wave Lithotripsy in Rhode Island

Procedure Has Permanently Altered the Treatment of Urinary Calculi

August Zabbo, MD

David L. Clair, MD

Barry S. Stein, MD

Recent technologic advances have obviated the need for open surgical procedures in most cases of renal and ureteral calculi. Percutaneous methods of renal calculus extraction were advanced and disseminated in the early 1980s. Ureteral calculi have similarly been approached with ureteropyeloscopes, which are passed transurethrally to endoscope the entire course of the ureter, at which time a calculus can be visualized and extracted. Such procedures employ ultrasonic or electrohydraulic lithotripsy, which use contact probes to deliver energy to fragment calculi prior to their removal. These procedures completely changed the urologic management of renal and ureteral calculi, markedly decreasing hospital stay and recovery time compared to traditional surgical procedures. As revolutionary as these so-called "endourologic" techniques are, they have already largely been replaced by extracorporeal shock wave lithotripsy (ESWL). Pioneered by the Dornier System, GmbH, the first human subjects

were treated in Munich, West Germany by Christian Chaussy in 1980. Introduction into the United States began on an experimental basis in February of 1984. United States Food and Drug Administration (FDA) approval of the technique and the Dornier lithotriptor was gained in December of 1984.

The Dornier lithotriptor uses electrically-generated focused shock waves to fragment calculi without any bodily invasion. A brief description of the clinical shock-wave procedure follows. For further technical and developmental information, the reader is referred to the monograph by Chaussy et al.¹

Anesthesia is currently required for ESWL; either regional or general anesthesia is suitable. We favor general anesthesia with high-frequency low-volume ventilation, as this decreases the movement of the calculus with respiratory excursion. The patient is strapped into a special gantry to facilitate proper stone positioning and prevent motion. The gantry is brought over a 37°C waterbath which houses the shock-wave electrode and generator. The patient is then lowered into the bath. Stone location is estimated from previous radiographs, and the gantry is moved to place the calculus as close as possible to the shock-wave focus. Guided by bi-plane fluoroscopy, the urologist moves the stone into the exact shock-wave focus point. The shock-waves are then administered using electrocardiograph (EKG) monitored triggering to prevent cardiac arrhythmias.

The action of the shock waves on the stone and stone localization are periodically checked using fluoroscopy or still images on the fluoros-

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copy screen. When the stone is seen to be adequately fragmented or when an arbitrary maximum number of shocks is reached, the procedure is terminated. After the usual post-anesthesia recovery period, the patient is discharged home or to his room.

This paper describes our initial experience with ESWL in Rhode Island and discusses the application of this technology in the current management of urinary calculus disease.

MATERIALS AND METHODS

Sixty-six patients underwent 78 ESWL treatments for 67 urinary stones from March 10 to June 30, 1987. For the purposes of this report multiple stones in the same kidney are assessed as one stone. All treatments were carried out on a Dornier HM-3 ESWL mobile unit at the Rhode Island Hospital. Evaluation and treatment of all cases was carried out by one of two authors (AZ or BSS). Ureteral stents were placed prior to



Fig 1: Renal pelvic stone with ureteral stent in place prior to ESWL.

ESWL (Fig 1) if the stone was in the ureter, impacted at the ureteropelvic junction, or larger than two cm in diameter. By these criteria, 32 of our initial 66 patients had stent placement prior to ESWL in general, reflecting the large stone burden in our initial patients. Four patients had percutaneous nephrostomy tubes placed to relieve acute obstruction prior to referral for ESWL. Forty-four of the initial 78 treatments were carried out on inpatients, and 34 on outpatients.

All patients had intravenous urograms or plain abdominal radiographs and renal scans prior to ESWL (Fig 2). Pre-procedure laboratory workup included complete blood count (CBC), electrolytes and clotting profile. EKG and chest x-ray studies were obtained when appropriate. Post-ESWL, the patients had a CBC in the recovery room. Plain radiographs were obtained one day and one week post-ESWL. Follow-up intravenous urograms or renal scans were obtained one month after the procedures. Follow-up information on those patients not followed directly by one of the authors was obtained from the referring urologist by questionnaire.

Patients were determined to be "stone-free" if no calculi were visualized on follow-up radiographs after three months. The minimum criteria for success include 1) no retained ureteral fragments, 2) no retained fragments greater than 0.5 cm in diameter, 3) no persistent symptoms from retained fragments, and 4) no need for ancillary urologic procedures for retained fragments.

RESULTS

Follow-up information was available for 65 patients. The patient lost to follow-up is not included in this analysis, although his stone appeared well-fragmented on the first-day post-ESWL radiograph. Fifty-five patients were treated with a single ESWL treatment, ten patients required two ESWL treatments, and one patient had three ESWL treatments during the study period.

Successful treatments (as defined above) are tabulated according to stone size and position in Table 1. Overall, a 90 per cent success rate was obtained; larger stones and stones in the ureter tended to have a slightly lower success rate. The number of shocks delivered per treatment ranged from 500 to 3000 shocks with a mean of 1850 shocks. Larger or impacted (ie ureteral) stones generally required larger numbers of shocks. In general, those stones requiring more than one treatment were the larger renal pelvic stones and

Table 1. Success/Total (% Successful)

Stone Position	Stone Size			Total
	<1 cm	1-3 cm	>3 cm	
Calyx	7/7 (100%)	7/7 (100%)	1/1 (100%)	15/15 (100%)
Pelvis	11/12 (92%)	12/14 (86%)	8/10 (80%)	31/36 (86%)
Ureter	8/10 (80%)	5/5 (100%)	0/0	13/15 (86%)
Total	26/29 (90%)	24/26 (92%)	9/11	59/66 (90%)

Table 2. Stone Free/Total (% Stone Free)

Stone Position	Stone Size			Total
	<1 cm	1-3 cm	>3 cm	
Calyx	6/7 (86%)	3/7 (43%)	1/1 (100%)	10/15 (86%)
Pelvis	8/12 (66%)	7/14 (50%)	2/10 (20%)	17/36 (47%)
Ureter	8/10 (80%)	5/5 (100%)	0/0	13/15 (86%)
Total	22/29 (76%)	15/26 (57%)	3/11 (27%)	40/66 (61%)

staghorn calculi. Stone-free rates are tabulated in Table 2. By definition, successful ureteral calculus cases must be stone-free. In the case of renal, pelvic and calyceal stones the larger the stone burden, the more likely that residual fragments will remain.

Seven patients were classified as unsuccessful. Two patients had incomplete treatments, secondary to technical problems. One of these had ineffective epidural anesthesia, while the other had early termination of the procedure because of a malfunction in the EKG triggering of the shock waves. Both of these patients subsequently had successful ESWL treatments after the study period, but are included as unsuccessful in this series for statistical purposes. In two patients with ureteral stones, ESWL failed to fragment the stones. One patient underwent surgical ureterolithotomy, while the other had ureteroscopic manipulation and stone extraction. One patient with a staghorn calculus had retained fragments greater than 0.5 cm. He is currently asymptomatic and is being followed by his urologist. Two patients with initial renal pelvic calculi required post ESWL ureteroscopy for removal of retained ureteral fragments.

The complications in this series comprised febrile urinary tract infections in two patients. One patient responded promptly to antibiotics, while the other required percutaneous nephrostomy for acute obstruction and later ureteroscopic removal of ureteral fragments. One patient had a clinically significant decrease in hematocrit (from 40 per cent to 29 per cent) post-ESWL. No patient required transfusion. None of the patients treated as outpatients required re-admission for any reason.

DISCUSSION

Shock-wave lithotripsy has permanently altered the treatment of urinary calculi. Contraindications to the procedure include pregnancy, un-



Fig 2: Day 1 post ESWL showing fragmentation of stone. Patient eventually passed all fragments.

corrected bleeding disorders, and anatomic obstruction of the urinary tract distal to the calculus, which would require surgical repair. Cardiac pacemakers can be affected by shock waves, but there are maneuvers to protect them from malfunction during lithotripsy. The patient gantry in the current unit will not accommodate patients over 300 pounds in weight. Therefore, massively obese patients may not be treatable by this means. Children over 30 pounds in weight can be treated with a specific pediatric adjustment to the gantry.

More than 90 per cent of stones can be treated by ESWL. The success of treatment is related to several factors, the most prominent of these being stone composition, stone location, and stone burden. Calcium oxalate dihydrate, struvite, and uric acid calculi are readily fragmented by ESWL while cystine and calcium oxalate monohydrate stones are less readily fragmented. Renal pelvic stones can be fragmented more than 95 per cent of the time, while the success rate is decreased to approximately 80 per cent in ureteral stones.² Thus, attempts at dislodging ureteral stones into the renal pelvis are worthwhile. Our current approach to upper ureteral stones is to dislodge them into the renal pelvis with ureteral catheters. If this is unsuccessful or if the stone has been present for more than six weeks indicating likely impaction, ureteroscopy is carried out with an attempt to extract the stone through the ureteroscope or fragment it with ultrasonic lithotripsy. If this cannot be accomplished, the stone is pushed back into the renal pelvis and then fragmented with ESWL. Although this approach can also be applied in lower ureteral stones, they are much more amenable to ureteroscopic extraction.

Calculi greater than three cm in diameter are less likely to be successfully fragmented and passed after one ESWL treatment. The ESWL can be repeated if large fragments remain in the kidney, or ureteroscopic extraction can be carried out if the fragments remain in the ureter. The need for multiple procedures in large stones has led some authors to propose debulking of large stones with percutaneous nephrostolithotomy prior to ESWL.³ If the patient was not rendered stone-free by percutaneous nephrostolithotomy, residual fragments could be treated with shock-wave lithotripsy. Our own approach has been somewhat different in that we have tried ESWL first on large stones. We accept the fact that a second and even third procedure may be necessary. Occasionally, there will be massive stones greater than four or five cm in diameter

that would best be treated by open surgical removal or percutaneous procedures.

Defining success in ESWL procedures has been somewhat difficult. For the purpose of this report we have considered retained fragments requiring endourologic manipulations as treatment failures. However, these patients still have avoided the disability of open renal surgery, and it can be argued that endourologic procedures are an acceptable adjunct to achieve success. Since most centers report a 50-75 per cent stone-free rate, the importance of adequate follow-up is underscored. Retained ureteral fragments may be a source of chronic urinary obstruction and should be removed. Nearly all authors find some residual calyceal fragments acceptable as long as they are asymptomatic and not associated with chronic urinary tract infection. As plain abdominal radiographs and ultrasound may not reveal obstruction or ureteral stones, follow up must include some type of functional study such as intravenous urogram or renal scan. The cost-effectiveness of ESWL over standard surgical procedures has been well demonstrated, especially when the markedly shortened hospitalization and out-of-work time are considered.⁴ ESWL is comparable to percutaneous nephrostolithotomy in cost-effectiveness, but, as ESWL is much less invasive and carries fewer complications, it has rapidly become the preferred method of treatment for renal stones.

Several advances in shock-wave technology are on the horizon. Already bathless systems are available. Localization using ultrasound to eliminate the radiation exposure to the patient is being investigated (currently radiation exposure during a typical ESWL procedure is equivalent to that received during standard fluoroscopic procedures such as barium enema or upper gastrointestinal series). Methods of generating and delivering shock waves with various properties are being tested to limit or eliminate the need for anesthesia. Competition among manufacturers is fierce and will likely lead to decreased cost of the devices. Competing with the extracorporeal lithotriptors are systems using laser fibers to generate shock waves with the fibers passed through the ureter up to the stone. Because of markedly decreased costs in manufacturing such systems, they may replace extracorporeal lithotriptors to some degree. The revolution in the treatment of urinary calculus disease continues and urologists and other physicians involved in their treatment should keep abreast of these developments.

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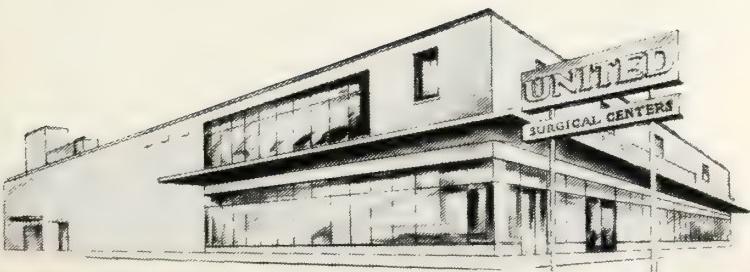
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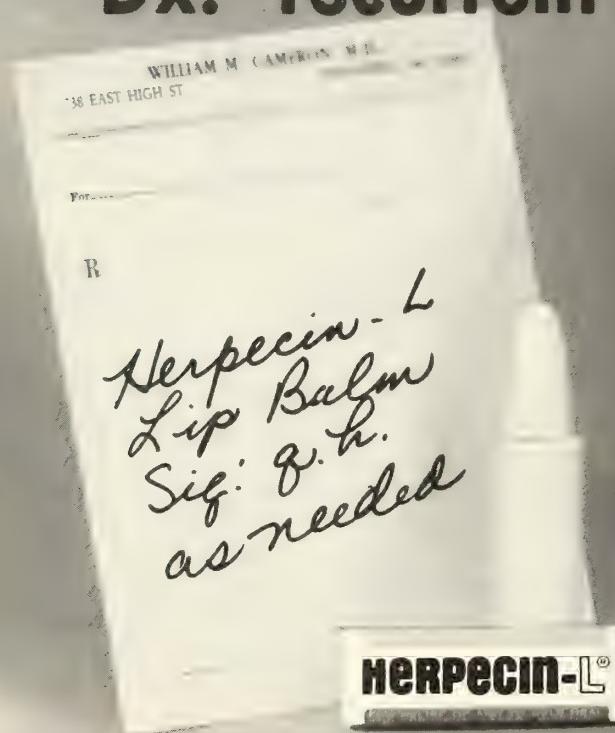
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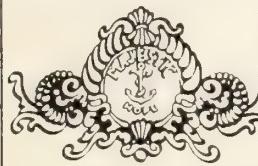


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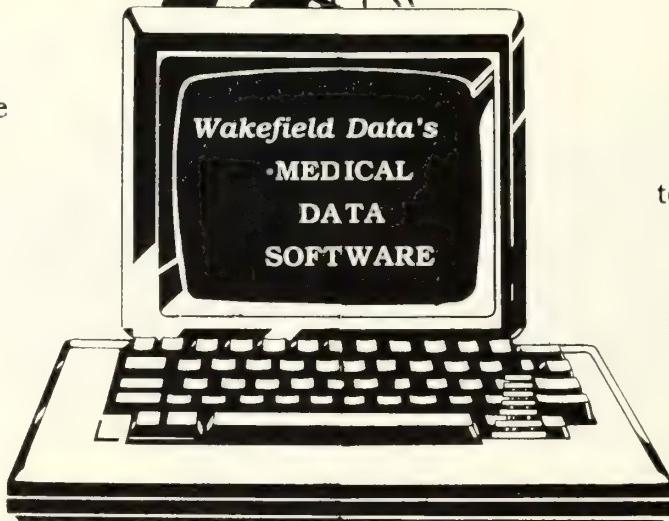
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AMA Report of the Board of Trustees

Nursing Education and the Supply of Nursing Personnel in the United States

There are 1.9 million registered nurses (RN) in the United States. In addition there are over 750,000 licensed practical nurses (LPN); therefore it is reasonable to say that the potential work-force of all nurses, RNs and LPNs, numbers about 2.5 million.

About 1.5 million RNs are in the work force either part time or full time; about 68 per cent are employed in hospitals.¹ The remainder are employed in the community, in public and proprietary home health agencies, and in a variety of settings such as insurance agencies and academia. The number of certified nurse practitioners and clinical nurse specialists is difficult to confirm due mainly to problems of definition, but it is estimated that there are at least 10,000 in the United States. In hospitals 71 per cent of the nurse force are technical nurses with associate degree/diploma preparation. LPNs are employed in larger proportions by Veterans Administration hospitals and smaller community hospitals. In nursing homes LPNs outnumber RNs four to one.² Only 7.1 per cent of all RNs work in nursing homes.³

Nursing education is presently comprised of four levels: the 12-month licensed practical nurse (LPN), the two (academic) year associate degree nurse (ADN), the three-year hospital-based or diploma nurse (Diploma), and the four-year baccalaureate nurse programs. Four-year collegiate education awards a bachelor of science degree (BSN) in nursing.

At the Interim Meeting of the American Medical Association House of Delegates held in Atlanta, GA, December 6-9, 1987, action was taken to adopt steps recommended in the following report to alleviate the widespread nursing shortage.

Registration to practice nursing (RN), can be obtained through the same board examination taken by the ADN, diploma, and the four-year baccalaureate nurse. License to practice as an LPN is acquired through a special examination. All licensure examinations are produced and monitored through the National Council of State Licensing Boards. All programs in nursing education, including LPN, ADN, Diploma, and BSN are accredited through the National League for Nursing (NLN), which claims educational activities as its professional prerogative.

The American Nurses Association (ANA) certifies about 45 per cent of clinical nurse specialists and nurse practitioners; otherwise ANA is not directly involved with education. The ANA expedites statutory changes in the state nurse practice acts such as those that are currently being promoted to restrict the RN licensure to four-year baccalaureate nurses. To date this change in the nurse practice acts has been vigorously and effectively opposed by practicing nurses in the state legislatures.

Historical Perspectives

Since 1868, the AMA has supported quality education for nurses.⁴ A shortage of nurses occurred after the first World War. In 1922 organized medicine urged the involvement of physicians in determining the curriculum for nursing education, accrediting programs, and teaching in schools of nursing. In the same year the AMA formed a Committee on Nursing and Nursing Education,⁵ which reported regularly to the House of Delegates until the depression years. In 1923 the Goldmark Report on nursing education,⁶ funded by the Rockefeller Foundation, stated that hospital-based Diploma nursing programs did not resemble those in educational in-

stitutions. It was noted that the work of student nurses in hospitals was in excess of necessary requirements for education and represented an apprenticeship that defrayed hospital costs. The report suggested that all education for nursing should be in university settings.

In 1933, the AMA cosponsored a joint study of medical and nursing schools with the National League for Nursing Education (NLNE), the American Hospital Association (AHA), and others. Seventy-nine medical schools were reviewed, as well as 2000 schools of nursing. Although about 40 nursing schools had university affiliations, diploma programs accounted for 98 per cent of all nursing schools at this time. The surplus of nurses that occurred in the early 1930s was viewed by the National League for Nursing Education as an opportunity to upgrade nursing educational programs, diminish recruitment, and limit the number of schools of nursing. As a result organized nursing planned to place all programs under nursing direction and to use only graduate nurses, when possible, at the bedside. Notwithstanding, in 1950 75 per cent of all classes in medical surgical nursing, pediatrics, and obstetrics were taught by physicians, and the majority of RNs were still diploma graduates.⁷

After World War II the shortage of medical and nursing personnel was critical. Community colleges emerged to promote easy access to education at low cost. The National League for Nursing Education recommended to the Association of Junior Colleges that a study be made of the feasibility of incorporating nursing education into their programs. In 1952 the two-year, post-high school, associate degree (ADN) programs began. About the same time, 12-month programs that started during World War II for licensed practical nurses were incorporated into some, but not all, junior colleges. ADNs were labeled as "bedside" nurses despite the problem of incorporating practical experiences into the 18-month curriculum.

In June 1953 a committee comprised of the AMA, the NLN, and the AHA, as part of a commission for Improvement of Care of the Patient, presented an eight-point program⁸ on nursing affairs that was approved by the AMA's House of Delegates. The report, besides confirming the post World War shortage of bedside nurses, approved the concept of providing methods of transition between the new and old educational programs in nursing. In 1952, as diploma schools continued to decline, the AMA again expressed its concern for availability of nurses as a medical

resource for quality bedside care.⁹ In 1958¹⁰ the AMA's House of Delegates approved Resolution 2, recommending physician participation in state Nursing Licensing Boards.¹¹ This resolution coincided with the successful initiatives by organized nursing to promote all-nurse licensing boards; however, the participation of physicians and nurses on state advisory committees was encouraged.

In 1965 the American Nurses Association stated that all nursing programs should be within the general education system. Diploma or hospital-based programs were considered unproductive to the independence required by any profession to govern its own educational concerns. In 1966 the ANA published a position paper supporting two levels of entry into nursing practice — the technical nurse with an associate degree and the professional nurse with a BSN or four-year degree.¹² Hospital-based programs and LPNs were to be phased out. While it was noted that LPNs made a valuable contribution to care in the absence of sufficient RNs, the ANA recommended the systematic replacement of LPN and Diploma programs with associate degree education.

At first the associate degree was viewed as an interim step to the baccalaureate program. Towards the end of the 1970s it became apparent that only 3 per cent of graduates from ADN programs and less than 10 per cent of diploma graduates continued their formal education to BSN status. Still, priorities for federal funding of nursing education were to be given to baccalaureate programs and graduate education of nurse specialists. The National League for Nursing expressed concern that the impact of this policy would diminish recruitment into all nursing programs of education and, for a time, supported four levels of education in response to the pressure from their constituencies. NLN reversed this position later and now supports two levels of entry into practice, the technical ADN and the BSN professional nurse; but discontent continues in the ranks to the present day.

The American Medical Association and the American Hospital Association viewed hospital-based nursing school programs as truly educational in character. Nonetheless, AMA actions during the late 1960s reaffirmed support for nursing programs at all levels, including higher education for leaders and teachers in nursing.¹³⁻¹⁵ There was special emphasis on the need to prepare bedside nurses, including LPNs, and the AMA supported improving salaries for RNs.

In the spring of 1970 the National League for

Nursing contacted the AMA at the request of the Council of Diploma Programs, a division of the League. AMA invited NLN and ANA to form an interorganizational committee to explore relationships between medicine and nursing. This committee was the precursor to the National Joint Practice Commission formed between AMA and ANA that was funded through the W. K. Kellogg Foundation and both associations.¹⁶ One of the first discussions of the committee addressed the AMA Board of Trustees Report Y (A-70) on "Medicine and Nursing in the 1970s."¹⁷ This report called for constructive physician collaboration with nursing and supported the concept of the physician led team. The report also recognized the need to expand the role of the nurse into clinical specialization. The report was considered by some nursing leaders to show lack of communication with medicine about the independence of nursing as a profession.¹⁸

In July 1980 in response to Substitute Resolution 78 (A-79) a report on nursing education reaffirmed AMA's policy to support all levels of nursing education.¹⁹ The report quoted an NLN survey²⁰ (1979) showing that 75 per cent of all practicing RNs had initially graduated from hospital based Diploma programs; it was this pool of nurses that was most likely to practice in physicians' offices. At that time recruitment into all nursing programs had declined 2 per cent and a shortage of nurses giving direct patient care was recognized by organized medicine as urgent. It was estimated in 1978 that 10,000 nurses were titled practitioners, and a further 15,000 were called clinical nurse specialists. Concern was expressed by the AMA that diploma education was being discontinued before an adequate supply of RNs had been secured to meet the needs of hospitalized patients. As a consequence, Resolution 10 (A-81) was adopted by AMA's House calling for the education of medical-surgical nurses devoted to direct patient care.²¹

In 1981 the National Commission on Nursing (NCN) was convened. The NCN was an independent, multidisciplinary commission funded by the American Hospital Association. It met just after the Institute of Medicine (IOM) began its study of the need for federal funding for nursing education and was charged with developing action plans for the future of nursing. The NCN recommendations were reviewed by the AMA's House in 1982.²² The NCN supported increased mobility through linkage between the educational programs in nursing, because this goal had not been perceived as effective in the past.²³ The

commission also recommended that shrinking private and federal funds should be allocated to ensure adequate numbers of nurses in BSN and graduate programs. Since then, the AMA House of Delegates has maintained its policy of support for all levels of nursing education.

Other Facts on Nursing Education

There is some evidence that increasing the level of education of nurses provides options that remove them from the bedside.^{24, 25} The preparation of bedside nurses was not the original purpose of baccalaureate education. Originally, advanced education for nurses was intended to promote leaders, managers, and public health nurses for community services. As patient services in hospitals have become more complex and highly technical, the clinical nurse specialist role with a master's degree has been developed to fill the need for complex clinical care at the bedside. Nursing faculty are increasingly working in practice settings to prepare clinically oriented nurses.

New BSN and ADN graduates usually require some hospital in-service education for bedside responsibilities before entering practice. Approximately 50 per cent of all BSN educational programs do not require experience in critical care units and few, if any, require operating room experience. BSN programs accentuate health maintenance, wellness, and leadership skills as well as traditional nursing skills. Clinical nurse specialists require a master's degree for certification in their area. Nurse practitioner status does not require the BSN in many states.

Nursing Personnel

The numbers of available nurses to meet the demands for nursing services vary in cycles; the demand for nurses increases in times of war and decreases in times of depression and recession. In the period of retrenchment in the late 1970s, a controversy arose regarding the need for further substantial federal funds to assure an adequate supply of nurses. The Institute of Medicine (IOM) published a report on Nursing and Nursing Education in 1983²⁶ in response to a congressional mandate.²⁷ The report stated that for 18 years (since 1965) \$1.6 billion was appropriated under the Nurse Training Act programs, established for the purpose of improving the quality and distribution of nursing personnel. There was expressed public need for more "generalist" or "bedside" nurses. No further federal support was suggested to increase the overall supply of nurses; however, it was recommended that funds to al-

leviate specific kinds of nursing shortages and maldistributions to medically underserved populations and to the elderly should be made through public and private sources. The report recognized that estimates of future need varied with methods of measurement and recommended that market forces control the types of nurses required for each setting. According to the IOM report, two factors had made allocation of resources for levels of nursing education difficult: 1) the lack of evidence of the effects on performance of different types of nursing education, and 2) the lack of definition of the scope of practice for different programs of nursing education. These omissions made it difficult to identify the demand for nurses with different competencies. The National Commission on Nursing, studying the same questions, published similar but more global recommendations shortly after the IOM report; these recommendations are now being implemented through the National Commission on Nursing Implementation Project (NCNIP). At this time NCNIP supports two levels of nursing education and the exclusive funding of baccalaureate programs and higher education for clinical nurse specialists/nurse practitioners.

In 1986 the Division of Nursing at the National Institute of Health reported that, on the whole, there was a balance between the demand and supply of nurses, and this situation was expected to extend into the 1990s. The nursing profession, alarmed at the decrease in enrollments in all nursing education programs, predicted a future shortage and questioned the Division of Nursing report. Almost simultaneously it had become apparent to physicians that a shortage of bedside nurses was causing the closure of critical care units and medical surgical beds in many areas of the country. Vacancies in hospitals were documented by surveys conducted by the American Hospital Association. Only 17.6 per cent of hospital surveys reported having no RN vacancies in 1986-1987.²⁸

Many reasons for the present shortage of nursing personnel at the bedside have been advanced. Lack of incentives for nurses to remain in hospital or to be recruited into the nursing profession are often cited as reasons for the shortage. A repeated theme is the compressed range of salaries for nurses. The beginning salaries in hospitals are accepted as reasonable, an average of \$20,000 per year; but for hospital nurses, including head nurses, even after years of service, the salary is compressed below \$40,000. This is-

sue is complicated by the fact that 1) nursing care costs are the largest ongoing item in hospital budgets, 2) there is little salary differential for technical and professional nurses as the BSN nurse seldom gets much more for clinical hospital practice than ADN and Diploma RNs, and 3) health care costs must be competitive in the present health system. A salient reason is that the prospective payment system has curtailed the length of stay in hospital and increased the number of acutely ill patients. This has precipitated the need for qualified nurses at the bedside.

There are deterrents to nursing recruitment. The American Health Care Association expressed its concern that limiting entry to two levels of nursing education leading to nursing practice may adversely influence entry into the field. Another deterrent to nursing recruitment is the lack of upward mobility in nursing. The 1983 Institute of Medicine study of nursing education, in order to encourage interest in entering the field of nursing, strongly recommended the "ladder" concept, the linkage and easy transition from beginning nursing programs to higher education. The concept has encountered many barriers to effective implementation.

Other reasons presented for the shortage of bedside, medical-surgical nurses are as follows: lack of status of the nursing profession; lack of incentives from within and without nursing to remain at the bedside; and lack of ability of nursing to compete for baccalaureate students with programs for other professions, notably law and medicine, especially in an era of reduced numbers of high school graduates eligible for college. The decline in enrollment in all nursing programs has been seen in BSN programs disproportionately. At least two baccalaureate nursing programs have closed in the past year. The future portends a continuing decline in the supply of nursing personnel should these trends continue.

Summary

For over 140 years organized medicine has been concerned with nursing education and its influence on the availability of nurses to monitor medical procedures at the bedside. Up to the second World War, education for nursing care as a medical resource for care of the sick and maintenance of the well was influenced strongly by physicians. Throughout this century nursing has diligently pursued professional status and the independent control of nursing education that is a prerequisite to professionalism. The AMA's concern is that

there will be adequate numbers of well-prepared nurses and caregivers available at the bedside to provide patient care. Nurses are a critical medical resource in delivery of modern care.

The decline of hospital-based programs is evident in the number of yearly graduates. It was estimated in 1984 that 14 per cent of RNs graduated with diplomas, 52 per cent held associate degrees and 33 per cent of all RNs held bachelors of science degrees in nursing.²⁹ Two-thirds of all nurses in the United States are prepared as technical nurses and one-third as professional nurses with BSNs. By the year 2000, it is planned that all education in nursing will be associate degree, (technical) or baccalaureate (professional) programs.³⁰

In general, shortages in nursing personnel have been cyclical; however, the shortage of nurses in long-term care facilities and rural hospitals is a chronic problem. The present vacancies in acute care settings impacts both private and public hospitals. The shortage occurs mainly in the areas of medical-surgical nursing, the operating and emergency rooms, and particularly in intensive care units although the problem of staffing critical care units has been growing for some time. In an era when there are more RNs and LPNs than at any other time in history, there is a critical shortage of bedside caregivers in acute and long-term facilities.

Since the Goldmark Report in 1923, the profession of nursing has been striving to provide qualified nurses through promoting programs within the collegiate system of education. At the same time nursing has developed professional independence and authority over its own affairs. The expanded role of the nurse is regarded as the means of providing status and justifying improved economic benefits for nurses. Since 1965 the American Nurses' Association has consistently and clearly stated its commitment to advance the baccalaureate nurse. Other major nursing associations agree that the "new professional nurse not only must care for patients but they must take on many of the monitoring and intervention activities once assumed by the physician."³¹ The commitment of the major nursing organizations to the funding and development of the baccalaureate trained and nurse practitioner/specialist can be expected to intensify in the next decade.³² Whether these initiatives will meet the needs of the public for qualified bedside nurses in all settings is in question.

The Board of Trustees recommends that the American Medical Association:

1. Support all levels of nursing education, at least until the crisis in the supply of bedside care personnel is resolved.
2. Support government and private initiatives that would facilitate the recruitment and education of nurses to provide care at the bedside.
3. Support economic and professional incentives to attract and retain high quality individuals to provide bedside nursing care.
4. Support hospital-based continuing education programs to promote the education of caregivers who assist in the implementation of medical procedures in critical care units, the operating and emergency rooms, and medical-surgical care.
5. Cooperate with other organizations concerned with acute and chronic hospital care to develop quality educational programs and methods of accreditation of programs to increase the availability of caregivers at the bedside and to meet the medical needs of the public.

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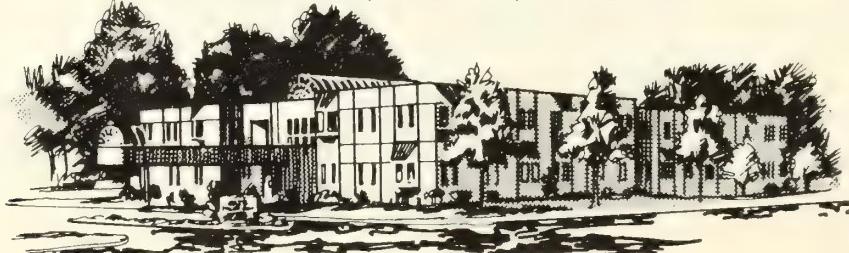
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Disease of Round Ligament of the Liver Simulating Acute Gall Bladder

Cases Presenting as Acute Surgical Emergencies Not Previously Reported

Anthony V. Migliaccio, MD

Surgical surprises are what make General Surgery so fascinating. We have encountered several such cases in the past. In our experience, however, we have never encountered in the operating room or in the perusal of the literature any mention of the abnormality presented by the following two cases.

Case 1

History. Mrs V. McD, 28 years of age, entered the Rhode Island Hospital with a history of agonizing pain localized to the right upper quadrant and midline of the abdomen. A white-blood-cell count was moderately elevated. A mass could be palpated, but not defined because of the marked tenderness. A diagnosis of acute cholecystitis was made, and treatment started with the expectation that surgery would be necessary. Cholecystography revealed a non-functioning gall bladder. Pre-operative diagnosis: Acute cholecystitis.

Operation. The abdomen was entered through a subcostal incision extending beyond the midline. Free bile was encountered. The gall bladder was thickened, but otherwise not remarkable. The round ligament of the liver extended from the umbilicus upward over the edge of the liver, was markedly enlarged and of greenish-yellow hue, and obviously contained bile. (Fig 1)

The peritoneum of the anterior abdominal wall was incised, so as to free this abnormal structure;



Fig 1. Case 1: Falciform ligament, containing a bile duct and showing acute inflammation and superficial bile staining.

and by blunt dissection it was followed to the edge of the liver. At this level it became tubular, and was dissected from the under surface of the right lobe of the liver, revealing a fibrous band crossing and constricting the proximal end of this dilated "tube." It was transected here, allowing further dissection toward the left hepatic duct, then twisted, and finally ligated at its junction with the left hepatic duct. With further dissection, the common bile duct was exposed, and a routine cholecystectomy and choledochotomy were performed with the insertion of a T-tube for decompression. A rubber tissue drain was placed down to the Foramen of Winslow. (Figs 2 and 3)

Hospital Course. Patient made an uneventful recovery.

Anthony V. Migliaccio, MD is a Consulting Surgeon at Rhode Island Hospital, Miriam Hospital, Women and Infants Hospital, and Westerly Hospital.

Pathology. The significant pathological feature in this case was the presence of biliary duct mucosal lining in the round ligament. Two photomicrographs document this finding — the first visualizing it at a low power of magnification; the second, at high power. (Figs 4 and 5)

All slides were reviewed by E. A. Boyden, Professor of Anatomy at the University of Washington School of Medicine, state of Washington. Quoting his conclusion: "My feeling is that the infiltration might have been due to the rupture of a larger branch of the left hepatic duct, where it lies in the vicinity of the point, where ligamen-

tum teres enters the liver. Compare with figure 536, Morris *Human Anatomy*, 11th Ed., 1953."¹

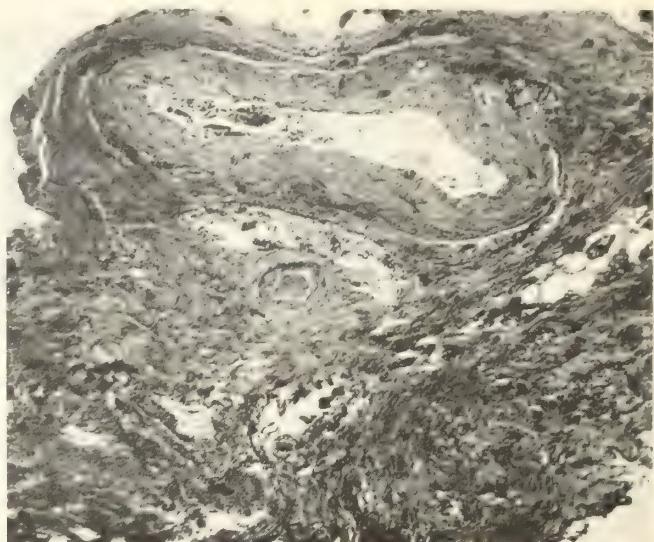


Fig 4. Case 1 (above): Photomicrographs of round ligament of liver. Under low power; showing biliary duct lining.



Fig 5. Case 1 (above): Under higher power; showing biliary duct lining.

Case 2

History. Mrs. E. W. was admitted to the Rhode Island Hospital with a history of localized right upper quadrant abdominal pain of two days' duration. No complaints of chills, nor of fried or fatty food intolerance. She has been running a low-grade fever during the illness.

Past History. Patient is a diabetic and has been on digitalis for the previous twenty years.

Physical Examination. Reveals an obese elderly woman with acute tenderness in the right upper quadrant of the abdomen and the contiguous epigastrium. Moreover, rebound tenderness is referred to the same areas. There is a suggestion



Fig 3. Case 1 (above): The round ligament narrows as it enters the left hepatic duct which could not be adequately visualized in photographs. The round ligament was ligated at the lowermost point visualized in this photograph.

of a palpable mass, questionable because of the interposing obese abdominal wall. The abdomen is moderately distended, but bowel sounds are present and active. There is no visible jaundice.

Laboratory Findings. White blood cell count was 15,500 with 83 per cent polynuclear cells, amylase 53, and a negative urinalysis, except for 1+ protein and 1+ sugar.

Operation. Through a right subcostal incision the gall bladder was found to be thickened, containing several stones, but showing no signs of infection. However, in the mid-line area, there was a mass, which proved to be a markedly edematous and gangrenous ligamentum teres (Fig 6).



Fig 6. Case 2: Clamp (arrow) points to infarction in round ligament.

This was carefully freed from the under surface of the anterior abdominal wall, and the dissection carried upward toward the liver, where the inflammatory structure was found to dip between the right and left lobes. Further dissection was needed to free it up and to excise it (Fig 7).



Fig 7. Case 2: Arrow points to gall bladder. Note empty area where round ligament was excised.

There was a tremendous amount of edema and induration in the area of the common duct and of the head of the pancreas. No stones could be palpated in the common bile duct.

Poor abdominal relaxation at this stage of the operation plus the marked inflammatory changes encountered made cholecystectomy too hazardous. Discretion being the better part of valor, cholecystostomy was considered the procedure of choice. The gall bladder was opened, two large stones were removed, and a large catheter inserted and secured into place. Stay sutures were added to the closure of the wound.

Hospital Course. This patient, like the previous one, made an uneventful recovery.

Pathology. The specimen in its fresh state consisted of an irregularly shaped piece of tissue measuring $10 \times 3.7 \times 2.1$ cm. Most of the surface was fairly smooth, varying in color from dark red to yellow, one-half of the cut surface being dark red — the other half yellow. Multiple cross-sections of the dark red surface showed areas of

whitish-gray, firm tissue, oblong in shape, and fairly well defined; whereas, others were brown, soft, and not well-defined.

Microscopic sections revealed hemorrhage, fibrin, and polymorphonuclear cells with a suggestion of a serosal surface.

Pathological Diagnosis. Fat and related tissue from the round ligament showing infarction and fat necrosis.

Discussion

Retiring from the active practice of surgery gave me the opportunity to review the records of my interesting and unusual cases. The first such case, previously reported in the *Rhode Island Medical Journal*,² was one of obstruction of the duodenum due to infiltration of its submucosal layer by calcium particles in sufficient quantity as to cause obstruction — certainly a surprising and unusual condition.

The two cases reported in this paper also present surprising and in both instances a unique condition. A search of the literature failed to produce any mention of the ligamentum teres causing surgical emergencies.

Acknowledgment

I wish to thank Doctors Anthony J. Migliaccio and John S. Dziob for their participation in the preparation of this paper.

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- ¹ Personal Communication: E. A. Boyden, Professor of Anatomy University of Washington School of Medicine, State of Washington.
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Information released from Hill and Knowlton reports that a topical antibiotic will soon be available by prescription for the treatment of impetigo, a contagious bacterial skin infection that affects more than 1.4 million Americans a year, mostly children. The drug is effective against the bacteria that causes impetigo, including *Staphylococcus aureus* and *Streptococcus pyogenes*. Dermatologists believe it will be easier for parents to treat their children because the antibiotic is applied directly to the infection site. Since this antibiotic is chemically unrelated to all other clinically approved antibiotics, the problem of cross resistance is also avoided. There is a lower incidence of side effects and allergic reactions than standard therapy which involves an oral antibiotic.

• • •

A letter appearing in April's *American Journal of Diseases of Children, AJDC* suggests parents often misunderstand a physician's instructions about medication for their children. Visits to a pediatric practice were studied by Gilbert Simon, MD, of the University of California-Davis Medical School, Sacramento. Simon says he carefully explained to each mother the child's diagnosis, information about the prescribed drug, when to expect improvement in the child's condition, and needed follow-up. The mother was then questioned by a student observer concerning the information and whether she felt distracted during the visit. The most common error made (from the results of 20 mothers making a total of 34 errors) was when to expect improvement. Many mothers apparently look for improvement too soon. Drug information was among other frequent mistakes. The mothers' ages and education had no effect on the error rate, but those judged by the ob-

server to be highly distracted were at greater risk of error. Suggestions offered by Simon to reduce misunderstanding included writing down drug dosage information, emphasizing the time to expect improvement, and minimizing chances for distraction.

• • •

Oral temperature for detection of malignant hyperthermia can be continuously reflected through the use of the new Redi-Temp liquid crystal thermometer. According to Medical Products of America, the unique elliptically-shaped Redi-Temp conforms to arterial and venous flow. Continual monitoring of the anesthetized patient's temperature is made quick and easy with the Redi-Temp liquid crystal temperature monitor. Redi-Temp, placed on the patient's forehead prior to surgery, will continuously and accurately display oral temperature in two degree increments from 94 to 106 degrees Fahrenheit in large numerals. The display changes with the patient's temperature, providing a fast, simple and non-invasive way to guard against undetected hyperthermia.

• • •

The expanded distribution and use of an experimental drug to treat *Pneumocystis carinii* pneumonia, a potentially life-threatening infection which often afflicts AIDS patients has been approved by the US Food and Drug Administration (FDA). In a statement from Hill and Knowlton, this is the first AIDS-related drug to be granted "treatment" IND — investigational new drug — status under the FDA's new regulations. The National Institute of Allergy and Infectious Diseases can now provide drug therapy to AIDS patients

with *Pneumocystis carinii* pneumonia who experience severe or life threatening adverse reactions to the conventional approved treatment drugs.

• • •

According to the May-June issue of *Arthritis Today*, researchers at University of Pennsylvania may have identified the substance that triggers scleroderma, a disease in which the body produces damaging amounts of connective tissue. Researchers John Varga, MD and Sergio A. Jimenez, MD grew normal skin cells called fibroblasts in the laboratory. When they treated these cells with a naturally occurring substance called transforming growth factor beta (TGFB), the laboratory cells behaved much like skin cells of people with scleroderma by overproducing connective tissue. The findings of the research team suggest that TGFB acts as the beginning stages of scleroderma by activating genes in skin cells which speed up connective tissue production.

• • •

The Amyotrophic Lateral Sclerosis (ALS) Association reports that in studies conducted by Bernard M. Patten, MD, FACP, Baylor College of Medicine, Houston, Texas, some patients with ALS are showing symptomatic improvements. For ten months, Dr Patten gave 15 ALS patients L-threonine, an amino acid, doses from two to four grams daily with no ill effects. Within 48 hours improvements occurred including better voice, swallowing, less drooling, decreased fasciculations, increased energy and improved spasticity, the latter particularly noted in those with bulbar signs. Changes occurred more dramatically with those most severely affected. When substitutions of amino acids leucine or isoleucine as placebos were used, patients reverted to their previous condition. On returning to L-threonine, the physical manifestations of ALS were almost immediately eliminated. Of the fifteen patients in the study, seven made a definite improvement, three had minor improvement, and the remaining five showed no change at all.

ERRATUM

The author, John S. Dziob, MD, of the paper, "The Anatomy of an Experiment," *Rhode Island Medical Journal*, March 1988, Vol 71, wishes to call attention to a misstatement on page 106 of that same issue. This occurs in the description of the last leg of the journey across India to its East coast at Howrah, the railhead of Calcutta. We did not board a sidewheeler at Howrah but continued by rail northeastward to Gauhati, which is on the Brahmaputra River, and thence overnight on the boat to Dibrugarh, where we returned to the rail for Ledo and Margharita — the latter our jungle destination in the northeast corner of Assam and the foothills of the Himalayas. This in no way alters the total mileage as noted.

The "haze of forty years" becomes particularly dense at that phase of the peregrination, and I am grateful to Thomas Perry, MD, our colleague and fellow traveler, for picking it up and setting it straight.

John S. Dziob, MD

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PERIPATETICS

At the October 1987 Annual Meeting of the American Society of Anesthesiologists in Atlanta, GA, **Dr Moustafa A. El-Naggar**, Anesthesiologist-in-Chief at The Memorial Hospital in Pawtucket, presented his findings on a research study to reduce the severity of pain following surgery. **Dr El-Naggar** reported on the use of bilateral intra-pleural intercostal nerve block at the meeting of the International Anesthesiological Research Society held this past March in San Diego, CA.

• • •

Assistant professor of medicine at Brown University and head of the department of gerontology at Roger Williams General Hospital, **Dr Marsha Fretwell** has been elected to a three-year term on the governing council of the American Hospital Association's Section on Aging and Long-Term Care Services.

• • •

The American Association for Surgery of Trauma has elected **Dr Donald Gann**, professor and chairman of the department of surgery at Brown and Rhode Island Hospital, as president for the year 1987-88.

• • •

Dr Charles Cutler, clinical instructor in medicine at Brown and senior vice president and chief medical director at Rhode Island Group Health Association presented a paper, "Evaluation Process for Expanding Multi-Site Organizations," at the China-United States Conference on Managing Hospitals in the 90s, held November 2-3 in Beijing, People's Republic of China, along with Stephanie I. Hunter, RIGHA's director of professional relations.

• • •

At the Louisiana State University Medical Center 1987 Sports Medicine Lecture Series in New Orleans, **Dr Paul D. Thompson**, associate professor of medicine at Brown and Miriam Hospital, appeared as a distinguished lecturer. **Dr Thompson** is also one of eight US physicians who have been named to a Sports Medicine Advisory Committee established by the US Olympic Committee to improve national cycling team performance.

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Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

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References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
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4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or

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without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency.

Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene and leukopenia, thrombocytopenia, agranulocytosis and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide. Dose adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine.

Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components.

Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The

following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as chlorthalidone-induced hypokalemia. Concurrent use with chlorpropamide may increase the risk of severe hypotension. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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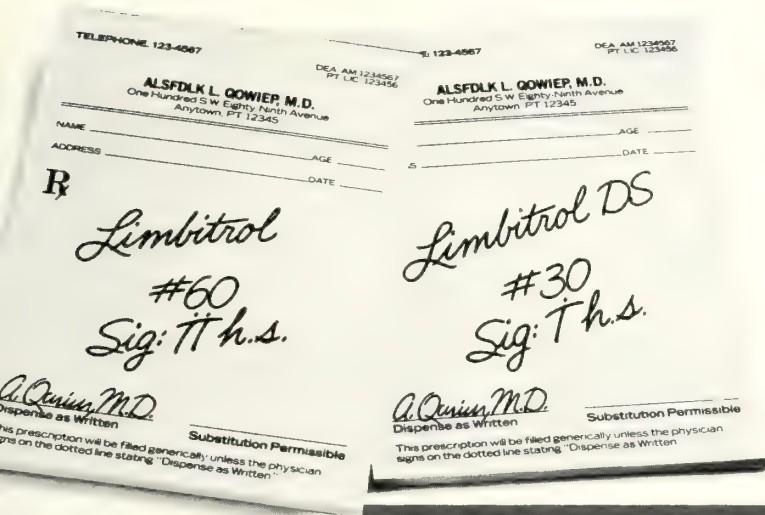


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Warnings: Use with caution in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur when used with anticholinergics. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia, prolongation of conduction time, myocardial infarction and stroke reported with tricyclic antidepressants, especially in high doses. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs: **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. **Neurologic:** Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extra-pyramidal symptoms, syncope, changes in EEG patterns. **Anticholinergic:** Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. **Allergic:** Skin rash, urticaria, photosensitization, edema of face and tongue, pruritis. **Hematologic:** Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. **Endocrine:** Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Overdosage: Immediately hospitalize patient. Treat symptomatically and supportively. I.V. administration of 1 to 3 mg physostigmine salicylate may reverse symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

How Supplied: Double strength (DS) Tablets, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and Tablets, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.



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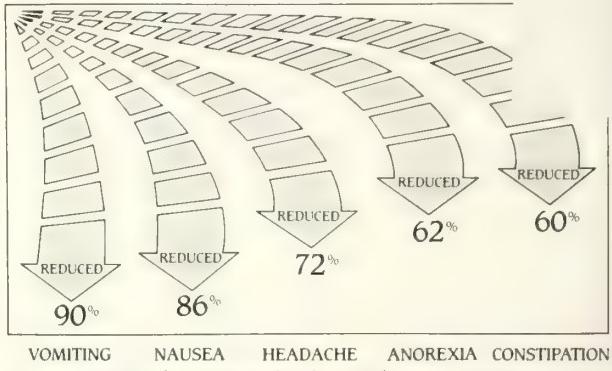
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Percentage of Reduction in Individual Somatic S. During First Week of Limbitrol Therapy*



*Patients often presented with more than one somatic symptom.

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Please see summary of product information inside back cover.

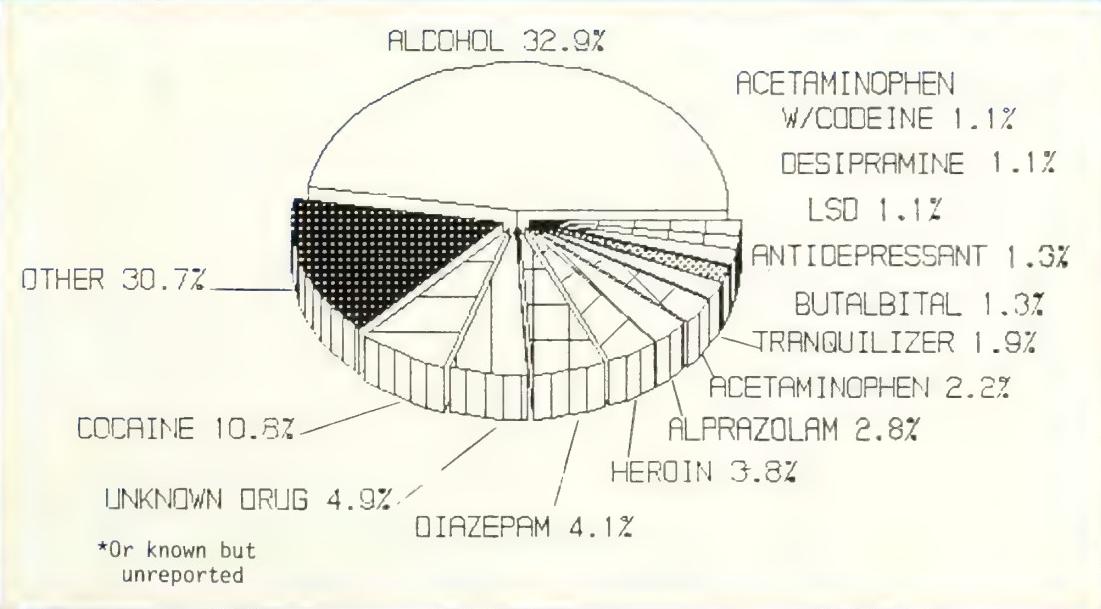


RHODE ISLAND MEDICAL JOURNAL



July 1988

Volume 71, Number 7



TOP-RANKING DRUG RELATED VISITS IN RHODE ISLAND EMERGENCY ROOMS (1987)

(See page 275)

FISKE PRIZE COMPETITION

The Trustees of the Caleb Fiske Fund invite readers of the RHODE ISLAND MEDICAL JOURNAL to submit nominations for the 1988 Fiske Prize Competition for scholarly writing in medicine.

Readers may nominate either their own work or meritorious works by other authors.

Eligible for consideration are scientific articles, essays and books published anywhere, or submitted for publication, during the calendar year 1987. Original manuscripts that have not been submitted elsewhere are also eligible.

The 1988 competition is limited to medical topics but is not restricted to any particular clinical, socio-economic, or historical area of medicine or surgery.

Submissions must be in English.

Copies of written work for consideration should be submitted to the

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Soldier being examined for effects of high-altitude cerebral edema.

ALLAN J. HAMILTON, M.D.

Neurosurgical Resident and Research Fellow,
Massachusetts General Hospital, Boston, Massachusetts.
Captain, U.S. Army Reserve.

EDUCATION Ithaca College, B.A. (Magna Cum Laude);
Hamilton College (Pre-med); Harvard Medical School.

RESIDENCY General Surgical Internship. Neurosurgical
Residency, Massachusetts General Hospital.

CONTINUING EDUCATION Neurology and Neuro-
surgery Research Fellowship Training, National Institutes
of Health.

OUTSTANDING ACHIEVEMENTS Olsen Memorial
Fellowship, National Masonic Medical Research Foundation;
Albert Schweitzer Fellowship, International Albert Schweitzer
Foundation; Harvard Medical School Cabot Prize for Best
Senior Thesis; recently published article, "Who Shall Live
and Who Shall Die" in Newsweek Magazine.

■ The work I'm doing in the Army Reserve fits perfectly with my academic research interests in civilian life. The Army is very concerned with the effects of high-altitude cerebral edema, which is a mirror model of cerebral hypoxia, something I deal with every day in our neurosurgical intensive care unit. I couldn't ask for a smoother transition. And that's true for a lot of Reserve physicians. All we really do is change our clothes, not our mindset.

"Some of the projects the Army is undertaking are on the cutting edge of research. For example, I'm currently involved in developing for the Army a prototype of a non-invasive intracranial pressure-monitoring device that we hope will allow us to measure pressure changes as the brain swells—without drilling holes in the skull. If we can get our design to work, such a device could revolutionize high-altitude medicine as well as civilian neurosurgical care."

"The quality of medicine and the caliber of people I've been associated with in the Army Reserve are, without question, equal to civilian hospitals. In fact, I'm giving serious consideration to applying for an active duty academic position in Army Medicine when my residency ends at Massachusetts General." ■

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WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplemental potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or

Not for initial therapy. See brief summary.

without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency.

Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine.

Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The

following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hypercalcemia and gout, digitalis intoxication (i.e., hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, tinnitus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient Pak™ unit-of-use bottles of 100.

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Volume 71, Number 7

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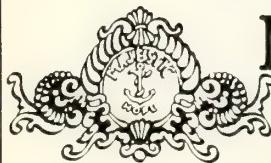


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*The Purpose of the Drug-Abuse Legislation is to Facilitate Law Enforcement, Rehabilitation,
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Gardner T. Swarts, MD

Cover: Graph depicting number and percentage of drug-related emergency room visits courtesy of Rhode Island Department of Health, Division of Drug Control. See page 275.

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Long-Term Care: A Growing Concern

Irving Berlin recently celebrated his 100th birthday. George Burns is booked to play the Palladium in London when he turns 100. Though these men are celebrities, they are prime examples of a host of elderly Americans who continue to enjoy vital lives. My own grandfather, an engaging man, is beginning his 96th year. However, many in the expanding over-65 population develop illnesses which require daily medical attention resulting in unplanned expenses that aren't covered by or far exceed their medical coverage. As the elderly population expands (the aging baby-boomer generation is responsible for this increase), the Medicare system in its present form does not address these needs. While the expanded Medicare "catastrophic" legislation currently working its way through Congress mitigates certain problems, it does not significantly ease the burden of prolonged chronic disability. The search for answers to long-term care financing is fast becoming an acute concern.

A survey initiated by the American Association of Retired Persons (AARP)¹ shows a surprising ignorance among the elderly as to what services Medicare will actually provide. Many assume it will adequately cover all of their health-care costs. Unfortunately, realization of the facts comes much too late — after a crisis has occurred which requires them to deplete their resources. Alice Rivlin, former director of the Congressional Budget Office, in a three-year study titled "Caring for the Disabled Elderly: Who Will Pay?" proposes immediate changes within Medicare. One recommendation is expanding coverage to include nursing homes and home-health services.

The issue is currently being addressed through legislation co-sponsored by Senator John H. Chafee of Rhode Island providing for long-term care.

Many concerned with the long-term care issues are looking to private sector involvement as a substitute for government spending. This is an underdeveloped concept offering great opportunities. Insurance companies are being encouraged to offer long-term care policies with a variety of options. Some of these programs are explored further through an AMA report in this issue of the *Journal*.

Over 44 per cent of all Americans over age 45 who have a parent or other relative still living list health-care costs as a primary concern.¹ As the need to secure financing for the elderly continues, it is important that individuals everywhere become aware of what their role in providing for this care can be. Most Americans are of the "enjoy now, worry later" mindset. From youth on we are attuned to instant gratification. Short-term results have always been easier to grasp than long-term goals. But, if we can respond by finding ways to save now (some examples are employer-offered coverage, long-term care savings accounts, tax-free retirement programs), perhaps the burden won't be so overwhelming when we reach that golden age.

Kimberly J. Allyn

References

- ¹ Health Care In America: Views and Experiences of Mature Adults. Prepared for The American Association of Retired Persons by Hamilton, Frederick & Schneiders, Washington, DC, 1987.

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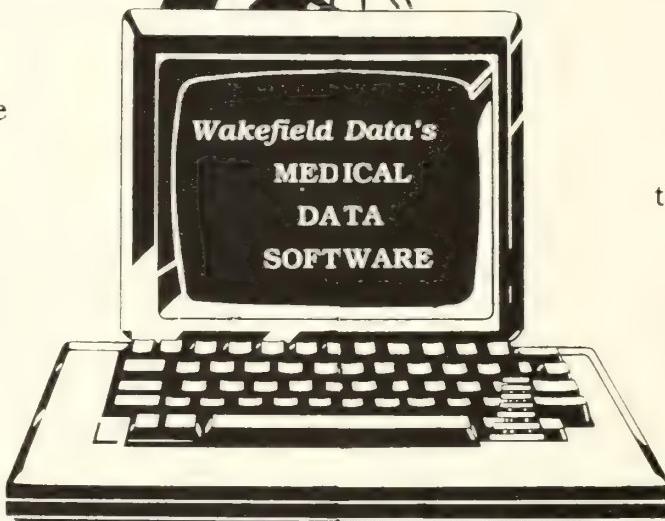
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EDITOR'S MAILBOX

Prescription Writing

To the Editor:

I should like to call your readers' attention to the following guidelines for prescription writing. A prescription is an order from a practitioner to a pharmacist to dispense medications to an ultimate user. The prescription, by law, must contain certain information, the absence of which creates difficulty and inconvenience for the patient and subjects the pharmacist to review by federal and state auditors.

Prescriptions must contain the name and address of the patient and the name and address of the prescriber. When substances are contained in Schedule II of the Uniform Controlled Substances Act a duplicate prescription, provided by the Director of Health, is required for prescriptions written in Rhode Island. Similarly, hypodermic needles and syringes must be ordered on the duplicate prescription form only.

The law also requires that each physician have their name clearly printed on the prescription form used, and that must be done, even in the emergency room, clinic, or hospital setting when the name of the institution might also be on the blank. Personalized prescriptions for Schedule II substances are supplied by the Director of Health upon registration. Finally, all prescriptions must contain two lines which indicate the prescriber's wishes with regard to generic drug substitution, with the line "Dispense as Written" being used when substitution is not permitted in the state.

Pharmacists want to help physicians execute their professional duties, while at the same time coping with drug diversion, the forged prescription and maintaining absolute accuracy in compounding orders. Taking a moment to supply the required information, or purchasing a simple rubber stamp to make old forms conform to state law, or otherwise taking a moment to supply this information by telephone will be a very important step in avoiding errors and will eliminate unnecessary phone calls to very busy offices.

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Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

Axid is indicated for maintenance therapy for duodenal ulcer patients, at a reduced dosage of 150 mg b.i.d. after healing of an active duodenal ulcer. The consequences of continuous therapy with Axid for longer than one year are not known.

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H₂-receptor antagonists.

Precautions: General—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions: No interactions have been observed between Axid and theophylline, chlorazepoxide, lorazepam, lidocaine, phenyltol, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur in patients given very high doses (3,900 mg) of aspirin daily; increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high dose males compared to placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement.

compared to concurrent controls, and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive, and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery is not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, and the mouse lymphoma assay.

In a two-generation, perinatal and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose, and in Dutch Belted rabbits at doses up to 55 times the human dose, revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White Rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Nizatidine is secreted and concentrated in the milk of lactating rats. Pups reared by treated lactating rats had depressed growth rates. Although no studies have been conducted in lactating women, nizatidine is assumed to be secreted in human milk, and caution should be exercised when nizatidine is administered to nursing mothers.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among the more common adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs <0.1%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to

determine whether these were caused by nizatidine.

Hepatic—Hepatotoxicity, evidenced by elevated liver enzyme tests (SGOT (AST), SGPT (ALT), or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and in a single instance, SGPT was greater than 2,000 IU. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antidiuretic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic—Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H₂-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs.

Integumentary—Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients. Rash and exfoliative dermatitis were also reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported.

Overdosage: There is little clinical experience with overdosage of Axid in humans. If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous LD₅₀ values in the rat and mouse were 301 mg/kg and 232 mg/kg respectively.

PV 2091 AMP [04/288]

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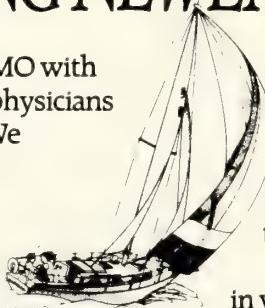
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AMA Report of the Council on Medical Service

Financing Long-Term Care

The elderly population in the US (65 years of age and over) is expected to more than double from 1980 to 2030; from 25 million persons or 9.9 per cent of the total US population, to 55 million, or 18.3 per cent of the US population. In addition, the age composition of the over-65 group itself is changing. Between 1980 and 1990, it is projected that the number of elderly individuals 65-74 years of age will increase by 13.8 per cent, those age 75-84 years of age by 26.6 per cent, and those 85 years and over by 20.1 per cent.¹

This unprecedented growth in the older population — particularly the 75-plus age group — will have a major impact on the nation's health care system. It is well documented that while elderly individuals today are generally healthier than elderly individuals of preceding generations, persons age 65 years and over utilize a substantially greater proportion of health care services than do the rest of the population. Although the House has already recommended a fiscally and actuarially sound proposal for financing the growing acute health care needs of the elderly (Board of Trustees Report MM, 1986 Annual Meeting), another critical policy issue affecting the care of both the elderly and a certain portion of the under-65 population in the coming year will be an increased need for the financing of long-term care services.

The term "long-term care" has traditionally been used to connote a broad range of both medical and supportive/custodial services for individ-

uals who have lost some capacity for self-care due to a chronic illness or condition, and who are expected to need care for an extended period of time. Long-term care services are often concerned with minimizing the effects of one or more diseases and with delaying deterioration of the person's functional capabilities rather than with curative or restorative goals.

While it has been estimated that approximately one-third of the long-term care population is under age 65, the need for long-term care strongly increases with age. In 1977, 89 per cent of nursing home residents were over 65 years of age.² According to the American Health Care Association (AHCA), an organization representing proprietary and nonprofit nursing homes, nursing home utilization also increases with age within the elderly population, from two per cent among persons age 65-74 years to 23 per cent of those 85 years and older.³ Similarly, it has been estimated that the percentage of the elderly needing personal care (ie, assistance with eating, toileting, mobility, bathing, dressing) increases from 2.6 per cent in the 65-74 year-old group to 31.6 per cent of those 85 years of age and older.⁴

Given the projected growth of the elderly population and current patterns in utilization of long-term care services, major increases in the demand for such services are anticipated. This fact has intensified pressure for the development of adequate mechanisms to finance these services for persons of all ages, since the expense of long-term care is becoming one of the leading causes of impoverishment.

Most of this nation's expenditures for long-term care are for nursing home or other institutional care. These expenditures are almost equally divided between public and private sources, with Medicaid picking up most of the former. Medicaid accounts for about 49 per cent

At the Annual Meeting of the American Medical Association House of Delegates held in Chicago, Illinois, June 21-25, 1987, action was taken to adopt the following report.

of the nation's long-term institutional care expenditures. This expenditure represents more than one-third of total Medicaid payments, and in some states accounts for almost two-thirds of the state's Medicaid budget. Private, out-of-pocket expenditures account for 48 per cent of long-term institutional care expenditures. Private insurance payments account for about one per cent of total national expenditures for long-term institutional care. Medicare, which only covers up to 100 days of post-hospital care in a "skilled nursing facility," accounts for only two per cent of these expenditures.

A significant portion of Medicaid spending for long-term institutional care is on behalf of individuals who have "spent down" to eligibility. It is estimated that half of all current Medicaid nursing home residents did not initially qualify for Medicaid, but spent down their income and assets to Medicaid levels while institutionalized.⁵

Description of Long-Term Care Services

Such health-oriented services such as skilled nursing care and physical, occupational and other rehabilitative therapies are those normally covered under traditional health insurance plans, and — when their duration is protracted — under the catastrophic expense portion of such plans. The type of personal, supportive and custodial services needed on an ongoing basis by persons who have lost some capability for self-care is the one for which private sector protection is largely lacking. Either or both types of services may be required on a continuing basis by "long-term patients." Within that context, the types of services which should be considered for coverage under long-term care financing mechanisms can be more specifically identified as follows:

- Institutional care
 - personal care services to assist individuals with the basic activities of daily living and help prevent further deterioration in physical and mental capabilities, such as providing assistance with mobility, dressing, eating, bathing, grooming, and socialization.
 - congregate living services — eg, meal preparation and service, housekeeping and room maintenance.
- Noninstitutional services adjudged by a health professional as needed to avoid more expensive institutional care.
 - personal care services as defined above.
 - homemaker services (eg, food prepara-

tion, laundry, shopping and light housekeeping).

- home delivered and/or congregate meals: nutritional meals for individuals who cannot prepare their own, either delivered to the home or provided in a communal location (eg, senior center, church, school).
- specialized transportation to medical and other needed services for individuals with personal mobility limitation.

Private Sector Initiatives

Although private sector involvement in financing long-term care is currently minor, there is increasing evidence of activity and experimentation. While private sector mechanisms have received increased attention primarily within the context of the growing number of elderly requiring long-term care, some of these approaches are potentially applicable to the needs of young long-term patients as well. In general, private sector initiatives for financing long-term care can be grouped under four main categories: indemnity insurance plans, managed care approaches, cash accumulation plans, and family support. These initiatives are discussed below.

Indemnity Insurance Plans. About 75 insurance carriers are currently marketing or developing long-term care insurance products and an estimated 200,000 policies are in force.⁶ Most long-term care insurers are marketing individual indemnity policies to pay a fixed amount for each day of service in specified institutional settings and/or for specified levels of intensity.⁷ These policies typically provide coverage for two to four years of institutional skilled nursing care and for institutional intermediate and custodial care, but for a lesser amount of time and at a lesser rate than skilled nursing care. Definitions of the different levels of care vary among carriers, however, and the amount of payment is usually based on the type of facility providing the care rather than on the level of care provided.⁸ Home health care benefits are also provided under some of these policies, but these benefits are often limited to the services of a private duty nurse.

Although there are several identifiable common characteristics among these plans, a comparison of their premiums is not possible, given the wide variety of features and benefits which could influence the premiums charged. In general, however, premiums for individual long-term care insurance policies are usually structured by age groups and reflect increasing risk with age.

The beginning age of issuance under these policies ranges from 50 to 65 years. Some policies set premiums at issue age and do not increase them subsequently for individual enrollees, while others increase premiums as enrollees grow older.

Long-term care insurers employ a variety of risk management techniques. Fairly common approaches include the use of waiting periods, prior hospitalization requirements, preexisting condition clauses, explicit exclusions, and health status screening questions. Few policies provide first-day coverage, but offer beneficiaries a choice among various waiting periods ranging from 20 to 100 days. Most policies also contain a three-day hospitalization requirement prior to covered confinement in a long-term care institution, with confinement being for the same illness or injury which required hospitalization, and beginning within a certain number of days (typically 30 days) after hospital discharge. Such prior hospitalization provisions are patterned after a similar Medicare requirement for coverage of skilled nursing facility care.

Preexisting condition exclusions or limitations are found in virtually all existing individual long-term care insurance policies. Most policies delay, or in fewer instances permanently exclude, benefits for services required as a result of an injury or illness diagnosed or treated at any time prior to the effective date of the policy. A few insurers, however, only apply this restriction to conditions treated within a specified time (eg, six months) prior to plan enrollment. The delay before benefits are provided for expenses resulting from a pre-existing condition ranges from 30 days to 12 months, depending on the policy.

In addition to exclusions or temporary limitations for preexisting conditions, policies also typically exclude coverage under specified circumstances or for selected illnesses. It is standard practice for long-term care policies to exclude coverage of expenses incurred outside the US, resulting from war or intentional self-inflicted injury, and caused by mental disease and disorder. Some of the policies, however, only exclude coverage for mental disease and disorder if the problems are without "demonstrable organic disease."

Another risk management technique employed by long-term care insurers involves the use of health status screening questions. Prospective subscribers of long-term care policies are usually asked questions regarding their health status which are designed to screen out those who would be at high risk in regards to their use of

benefits. The screening questions typically seek information regarding an applicant's record of prior institutionalization and specific illnesses. These questions vary among insurers in their level of detail and the previous time period which their responses must cover.

Two specific examples of long-term care indemnity insurance policies are those marketed by CNA Insurance Companies and the American Association of Retired Persons (AARP). In addition, Thomas E. Getzen, PhD, of Temple University has proposed a plan which combines long-term care insurance and a deferred annuity benefit. These plans are described briefly below.

- CNA Insurance Companies' Convalescent Nursing Care Plan

CNA has provided a health insurance product indemnifying nursing facility confinement since 1974, and approximately 30,000 policies are currently in force. Claim payments resulting from these policies in the last five years have totalled \$15.4 million.

Marketed primarily to individuals, CNA's Convalescent Nursing Care Plan provides a daily cash benefit of up to \$80 for medically necessary convalescent care, defined as skilled, intermediate or custodial nursing care services furnished under the orders of a physician in a licensed skilled or intermediate care facility. Benefits are provided for a stay of up to 1000 consecutive days for issue ages 60-79 and for up to 365 days for issue ages 80-84, with a lifetime maximum benefit of up to 1500 days. Unless otherwise assigned, benefits are paid directly to the subscriber.

Benefits can begin after a waiting period of 15, 30 or 90 days of nursing facility confinement. To receive benefits, confinement must commence within 30 days of discharge from a hospital following a stay of at least three consecutive days, and be for the same injury or illness which necessitated hospitalization.

Potential subscribers to CNA's plan are required to provide information regarding specific illnesses they have had and any confinements in a hospital, nursing home, or convalescent care facility they may have experienced within the previous five years. This information is used by CNA primarily to assign subscribers to a health risk category for premium purposes. Approximately 15 per cent of applicants are denied coverage entirely based on this medical history.

A preexisting condition clause in CNA's plan restricts benefits for conditions for which sub-

scribers received medical advice or treatment in the six months preceding the effective date of their policy. Most such conditions, however, are covered if confinement begins at least 90 days after the policy's effective date. Explicitly excluded from coverage are expenses for confinement due to injury or illness for which benefits are payable under a Workers' Compensation or Occupational Disease Act or Law, resulting from war, or due to mental, psychoneurotic, or personality disorders without demonstrable organic disease. The policy does state that expenses for mental condition of an organic origin, such as mental abnormalities resulting from an accident or Alzheimer's Disease, are covered.

CNA's long-term policy is guaranteed renewable; that is, a policy will not be cancelled except for lapsed premium payment. CNA does reserve the right, however, to change a subscriber's premium if the subscriber is given 30 days prior written notice and the premium rate for everyone in the subscriber's policy rating group in that state is changed. With this exception, premiums are set at the time the policy is issued and are not increased for individuals thereafter. Age of eligibility for the plan is 60. The policy rating group to which a subscriber is assigned is dependent upon the waiting period and level of benefit selected, and the subscriber's age and health status.

In the near future, CNA will also offer enrollees in its long-term care plan an option providing coverage for home health care. According to a representation of CNA, the company anticipates that features of this option will include a 120-day waiting period, a prior hospital or nursing home confinement requirement, and a lifetime maximum benefit of two years coverage. In addition, it is anticipated that, rather than an indemnity benefit, this option will be provided as a service benefit, with the plan paying customary charges for medically necessary home health care services up to a certain percentage of the maximum nursing home benefit payable.

● AARP/Prudential's Long-Term Care Policy

AARP began pilot-testing a long-term care policy, underwritten by Prudential Insurance Company of America, in late 1985. When the plan was test marketed to a random sample of AARP members in six states, 1200 purchased coverage, a response rate of only about half of one per cent.⁹

The test product offered subscribers nursing home benefits of \$40 per day (regardless of the

level of care required) following a 20-day waiting period and a three-day hospital stay, with a lifetime maximum of 1,095 days or three years. The policy also provided payment for home health personal and skilled care visits at \$20 and \$25 per visit after the first 20 visits, up to a maximum of 365 visits. Premiums ranged from \$180 to \$1140 per year, depending on the age of the purchaser, with the premium set at the time of purchase (minimum enrollment age of 50). The plan included a six-month delay of coverage for preexisting conditions. Potential subscribers were required to complete a medical questionnaire but only three per cent were declined coverage for medical reasons.¹⁰

In surveying its members in the six states who had received enrollment packages, AARP found that two-thirds of the nonpurchasers believed that they did not need this type of coverage. More than one-third of the nonbuyers erroneously believed that they were already covered for long-term care through Medicare and/or Medigap insurance.

Based on the results of its test marketing, AARP has recently revised its plan. The hospitalization requirement has been deleted, the duration of the nursing home benefit has been extended to four years, and the waiting period has been increased to 90 day/visits. In lieu of the prior hospitalization requirement, AARP/Prudential's Patient Assessment Unit — a case management process — will be used to identify and oversee the level of care needed.¹¹ This revised long-term care policy is again being test marketed in six states. Enrollment is being solicited by mail and local media advertising.

● Getzen's Proposed Longlife Insurance Plan

A plan which combines long-term care insurance and a deferred annuity has been proposed by Thomas E. Getzen, PhD, of Temple University. Getzen's proposal, "Longlife Insurance Plan," would enable a single person or a couple to participate in the plan by paying its premium either in a lump sum using a portion of their accumulated pension benefits from employment, and/or in monthly payments for life. In return, participants would receive indemnity payments for institutionalization in any level of facility that provides continuous nursing care such as a hospital, skilled nursing facility or state licensed nursing home after their first year of enrollment and 45 days of confinement. In addition, after age 75, participants would receive annuity payments regardless of their health status or living

situation. These annuity payments would be made in addition to any indemnity payments being made for nursing care.

As an example of the premium costs and benefits of this proposal, Getzen anticipates that for a lump sum payment of \$23,008 or a monthly payment of \$246, a single male age 60 could receive indemnity payments of \$66 per day for nursing home confinement and annuity payments of \$20,000 per year after age 75.

In discussions held with the Council, Getzen indicated that this proposal allows the provision of benefits which are large relative to premiums by balancing risks and reducing adverse selection. Participants at high risk who are likely to utilize the indemnity benefit for institutionalization are also more likely to suffer early mortality, reducing the plan's annuity payments. On the other hand, participants who are attracted by the annuity payments are less likely to be institutionalized. In addition to limited adverse selection due to the reduction in the number of annuitants through mortality, the deferral of annuity payments allows for the accrual of interest on the premium payments.

Getzen indicated to the Council that he does not include home health care benefits in his plan due to the difficulties he believes would be associated with determining entitlement for such services and his concern regarding the potential induced demand that availability of such benefits could create for these services. Getzen also indicated, however, that the annuity payments provided to participants after age 75 could be used to purchase home health care services.

Managed Care Approaches. In addition to financing and underwriting the cost of long-term care services, managed care plans also coordinate and directly provide such services. Social/health maintenance organizations and continuing care retirement communities are two different approaches to the managed care concept. In addition, Northwestern National Life Insurance Company is developing a product called Lifescope which will provide participants with managed care and benefits from birth to death. These three managed care approaches are briefly described below.

• Social/Health Maintenance Organizations

The social/health maintenance organization (S/HMO) is a managed system of health and long-term care services, whereby a single organization assumes responsibility for a full range of acute inpatient ambulatory rehabilitative, home health,

and personal care services under a prospectively determined, fixed budget. Essentially, a S/HMO resembles an HMO except that senior citizens comprise 100 per cent of its membership and longterm, as well as acute, care services are provided.

S/HMOs are currently in the experimental stage. Four S/HMOs began operating in early 1985 as part of a demonstration project funded by the Health Care Financing Administration (HCFA) and coordinated by Brandeis University. These four demonstrations, in Long Beach, California; Portland, Oregon; Brooklyn, New York; and Minneapolis, Minnesota are scheduled to end in 1988.

Elderly individuals residing in the geographic areas selected as demonstration sites who participate or are eligible to participate in Medicare Parts A and B are eligible to enroll in a S/HMO. Prepaid Medicare and Medicaid funds and member fees are used to finance the cost of the services provided. Medicare reimburses the S/HMOs 100 per cent of the average per capita cost it pays for traditional health care for the elderly living in that geographic area, rather than the 95 per cent reimbursement rate provided other HMOs. In addition, enrollees are charged a monthly fee ranging from \$25 to \$40 and pay some copayments and deductibles.¹² To help underwrite risk on the demonstration sites, HCFA is providing reinsurance for the three years of this project.¹³

A few commercial insurers are also exploring the possibility of offering a long-term care optional benefit to their HMO enrollees.¹⁴ Data from the four S/HMO demonstration projects will be useful to such insurers.

• Continuing Care Retirement Communities

Continuing care retirement communities (CCRCs), or lifecare communities, provide their residents with a range of residential and social as well as health services in exchange for an initial entrance fee or prepayment and, typically, an additional monthly fee. Estimates as to the number of such communities, which are located throughout the US, range from 300 to 600.¹⁵ Most CCRCs are affiliated with another institution, typically a nonprofit religious organization, although interest in their development is growing within the for profit sector.¹⁶

Both the level of benefits provided and prices charged vary considerably among CCRCs. Initial entrance fees range from \$60,000 to \$125,000 and up, and monthly fees are usually over \$1000.¹⁴ Similarly, although CCRCs do provide

residents with access to a continuum of care using on-site facilities, benefits range from full service to more limited service in terms of copayments and cost-sharing requirements. For example, chronic care services, such as skilled nursing care, may be provided either as part of a total paid package or for an additional charge over the usual monthly fee. In over half of the CCRCs, however, the monthly payment covers care in the community's nursing facility if it becomes necessary.¹⁸

- Lifescope

Northwestern National Life Insurance Company is developing an innovative program called Lifescope which would provide total managed care and benefits to individuals during their working years and into their retirement. As currently conceived, Lifescope would be a flexible, or "cafeteria-style" plan in which subscribers are guaranteed a set of core benefits — including acute medical care, life insurance and disability benefits — and then pay extra for additional coverage. The program is intended to allow subscribers to adjust their health benefits as their needs change with advancing age.

It is anticipated that Lifescope would be marketed to employers as an employee fringe benefit. In addition to paying the premiums required for health care coverage during their working years, employees, and possibly their employers, would make payments to an employee retirement fund. Payments to this fund would accumulate interest over the employees' working years and then be used to finance their health and long-term care needs during their retirement. Northwestern National envisions the employee retirement fund as portable, enabling those who change jobs to continue to invest in it.

In regard to the long-term care component of the program, a representative of Northwestern National indicated to the Council that emphasis will be placed on assisting individuals in maintaining their independence to the extent possible. In addition to coverage for institutional skilled, intermediate and custodial care, home health and other support services such as transportation, meal preparation, and home maintenance would also be covered.

Lifescope will draw on the S/HMO concept by contracting with organized provider delivery systems, such as HMOs and preferred provider organizations, to provide subscribers with total managed care. It is anticipated that participating

providers will agree to reduced rates and will share in the financial risks of the program. Northwestern National recognizes that it will have to contract with organized provider systems across the country, as retirees often relocate.

Cash Accumulation Approaches. In contrast to the indemnity insurance plans and managed care approaches discussed above, cash accumulation instruments involve little or no risk sharing. Rather, they provide individuals with a mechanism for saving money for their future long-term care needs. Home equity conversion, including sale/leaseback arrangements and reverse annuity mortgages, and health individual retirement accounts, are examples of such financing instruments and are briefly described below.

- Home Equity Conversion

Three-fourths of all households, headed by the elderly are owner-occupied, and the average equity for each elderly homeowner exceeds \$50,000. Even among the elderly poor, 65 per cent are homeowners and 22 per cent of the poor and 32 per cent of the near-poor have more than \$50,000 in net home equity.¹⁹ The purpose of home equity conversion mechanisms is to enable homeowners to convert their home equity into income while still living in the home. Such income could be used by the elderly to purchase long-term care services, particularly home health care in lieu of institutional care. Sale/leaseback arrangements and reverse annuity mortgages are the two basic types of home equity conversion.

In a sale/leaseback arrangement, a home is sold to a buyer, but the seller retains the right to rent the home for life. Typically, the buyer provides the seller with a lump sum payment. A reverse annuity mortgage (RAM) is a loan against the equity of a home that provides the borrower with monthly payments rather than a lump sum amount. Repayment of all principal and interest is deferred until the end of the loan term, the sale of the home, or the death of the borrower. According to one source, as of 1984, approximately 200 private reverse annuity mortgage transactions had occurred in the US.²⁰

- Health Individual Retirement Account

A health individual retirement account (HIRA) is another cash accumulation instrument which would be used by individuals to earmark personal savings for health care needs, including long-term care expenses, after retirement. The AMA already supports the expansion of the existing IRA mechanism to provide supplemental

funds for health care expense on retirement, as part of its proposal for financing the health care of the elderly (Board of Trustees Report MM, A-86). Under AMA's proposal, all individuals would be allowed to contribute a tax deductible amount of \$500 (\$1000 for husband/wife) to an IRA. The contribution limits would be adjusted annually.

After attaining eligibility age, any funds withdrawn from such IRAs for health care expenses would be tax-free. In addition, individuals below eligibility age who become permanently and totally disabled could also withdraw funds for health care expenses tax-free. Eligible health expenses would include, but not be limited to, health insurance premiums for "wrap-around" coverage of deductibles and coinsurance, direct payment of such cost-sharing amounts, or expenses of long-term care.

Family Support. The ability of the family (other than one's spouse) to contribute to the cost of nursing home care is rarely considered in determining Medicaid eligibility for nursing home payment. Some states have begun to explore mechanisms for imposing financial obligations on family members for nursing home care. Policy analysis in this area could focus on the advisability/feasibility of requiring relatives to pay a certain portion of nursing home services and of providing financial encouragement to families (eg, tax incentives or direct payments) to maintain their chronically ill relatives at home instead of placing them in a nursing home whenever possible.

Conclusion

Adequate mechanisms for financing long-term care for persons in all age groups are needed. Given the fiscal constraints being experienced by the public sector, it is likely that the private sector will play an increasingly important role in meeting this need. This report provides suggestions as to the types of services which could be covered in a long-term care financing program and describes a variety of both operational and proposed private sector initiatives for financing long-term care.

With this informational report as a base, future reports to the House of Delegates will identify the strengths and weaknesses of the identified private sector initiatives for financing longterm care and present recommendations on this issue. The Council on Medical Service, as well as other policy units of the Association, will continue to assist in formation of policy on this critically important issue.

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If you know a physician who can benefit from peer education in a particular area of medical practice, please write Dr. William Colaiace, Chairman, Peer Review Committee on Physician Competency, Rhode Island Medical Society, 106 Francis Street, Providence, RI 02903. For more information, call the Society at (401)331-3207. All referrals are held in strict confidence.

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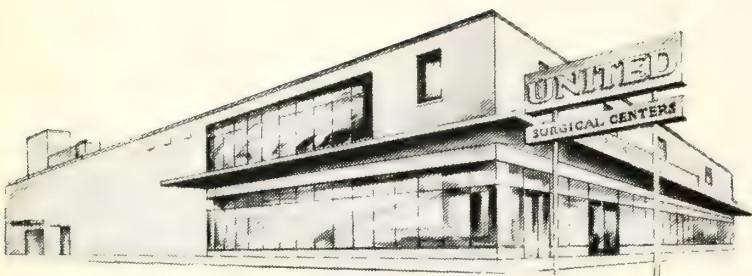
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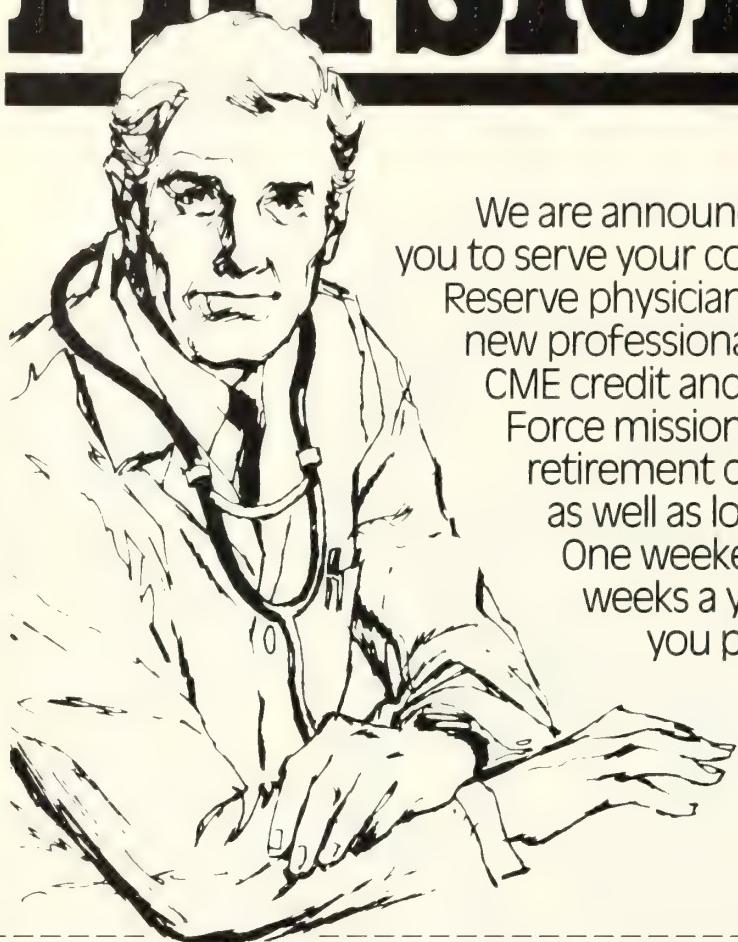
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An Annualized Analysis of Drug Related Incidents in Rhode Island Emergency Rooms — Calendar Year 1987

The Purpose of the Drug-Abuse Legislation is to Facilitate Law Enforcement, Rehabilitation, and Treatment in Drug Dependence

Charles Hachadorian, Jr, BS, MPA, RPh
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Diane A. Tellier, AS
Scott Andrews, AS
Walter Cataldo, AS

Title 21, Chapter 28.3 of the General Laws of the State of Rhode Island, titled "Drug Abuse Reporting Systems," was enacted into law as Chapter 263 of the Public Laws in 1972 to allow the Director of Health to compile relevant statistics regarding incidents of drug abuse. The legislative intent was to aid and assist law enforcement, rehabilitation, and social service agencies with the treatment of drug dependence.

Background

The act provided that data should include age, sex, occupation, background, and apparent de-

pendency. The data should contain the nature and type of drug involved, and the legislation required that all hospitals, physicians, and state and local law enforcement agencies report to the Director of Health monthly.

Section 21-28.3-3 requires the maintenance of confidentiality. Compilations of data and details of statistics may be released. This paper presents the first annualized statistical analysis of emergency room visits for incidents involving drugs of all types — controlled, legend, and non-prescription proprietary preparations.

An earlier prototype report¹ examined data collected during the period January 1979 through December 1986 (in two time frames, January 1, 1979 to June 30, 1986 and January 1, 1979 to December 31, 1986). The original report is cited for reference only, since significant statistical comparisons are not possible given the variability in reporting periods.

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Methodology

The "Report of an Incident of Drug Abuse" cards representing the period January 1 through December 31, 1987 were computerized and analyzed. The information on these cards was broken down into three parts, which consisted of information on the reporting agency, information on the patient, and the name of the drug or drugs that had caused the person to seek medical attention.

Reporting Agency. Part I of the form contained the name of the reporting agency, the address, and date of treatment. The reporting agency was assigned a code using the hospital pharmacy license number and the agency's zip code.

In the case of law enforcement agencies, reporting was nonexistent. Law enforcement agencies are also required to report to the Uniform Crime Reporting System of the Federal Bureau of Investigation, and much of the information is exactly the same as that required by this legislation. In the case of hospitals, response to the distribution of the prior study information has heightened awareness and compliance of effectiveness, resulting in 878 reports in 1987.

The Patient. The information on the reporting card consists of the patient's initials, occupation, age, date of birth, sex, race, and the city or town of residence. The patient's initials and occupation were not entered into the computer. With the new reporting year, however, the program has been updated to reflect the occupation, since it would be beneficial to know which occupations experience the highest rate of incidences of drug abuse, and whether those who are unemployed fall into the highest ranking category.

Results (Table I). Two major categorical areas are noteworthy and are offered herein without drawing conclusions. These are left to the reader, whose interpretations will be affected by his or her own experiences, practice locus, and specialty.

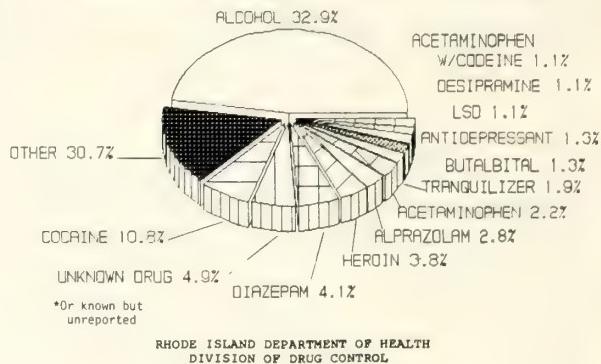
The first subject of concern is which agents most frequently cause persons to be sick enough in their judgment, or in the opinion of colleagues, to seek medical treatment at a hospital emergency room.

Alcohol ranks first on the frequency of reporting list (Table I) for 1987, with 289 incidents among 878 reports (ie 32.9 per cent of the cases involved alcohol).

Cocaine ranks second with 95 incidents, or 10.8 per cent of the total. The thirteen most frequently mentioned drugs (rankings 1-10), ac-

TABLE I
TOP-TEN EMERGENCY ROOM VISITS
January 1, 1987 - December 31, 1987

RANK	REPORTED INCIDENT	NUMBER OF INCIDENTS	PERCENTAGE
1	ALCOHOL	289	32.9
2	COCAINE	95	10.8
3	UNKNOWN DRUG	43	4.9
4	DIAZEPAM	36	4.1
5	HEROIN	33	3.8
6	ALPRAZOLAM	25	2.8
7	ACETAMINOPHEN	19	2.2
8	TRANQUILIZERS	17	1.9
9	ANTIDEPRESSANTS	11	1.3
10	BUTALBITAL	11	1.3
	ACETAMINOPHEN W/CODEINE	10	1.1
	DESIPIRAMINE	10	1.1
	LSD	10	1.1
	OTHER CAUSES FOR TREATMENT	269	30.7
	TOTAL INCIDENTS REPORTED	878	100.0



counted for 69.4 per cent of the drug-related incidents for the year (609/878).

Only seven of the 108 items mentioned at least once in the report are contraband — heroin ranking fifth on the overall list with 33 mentions; LSD ranking tenth with 10 mentions; marijuana ranking thirteenth with 7 mentions; hallucinogens as a group ranking eighteenth with 2 mentions, and mescaline, PCP, and Quaalude® all ranking nineteenth with 1 mention. In total, these amount to 6.3 per cent overall (55/878).

Ibuprofen, which ranked fifth with 8 mentions in 1987, should be monitored, since this drug is now over-the-counter, as well as legend, depending upon strength.

Patient demographics also are noteworthy. For example, alcohol patients ranged in age from 13-91, with males accounting for 193 cases and females 87 cases. The patient gender was not recorded on 9 cases. Race data were not reported in 258 of 289 cases.

Cocaine patients ranged in age from 14-47, with males accounting for 66 cases, females 28 cases, and one of unknown gender. Race was recorded as white in 44 cases, black in 38 cases, and 13 of other race.

The heroin age range was 20-46, with 23 males, and 10 females reported. The race identification was 18 whites, 8 blacks, and 7 "other."

The LSD patients ranged in age from 12-23, with 7 males and 3 females. Two were identified as black, one white and 7 of unknown race.

References

- ¹ Campbell, Norman A., Hachadorian, Jr, Charles: Report of drug related incidence in RI and analysis of emergency room data. International Narcotic Enforcement Officers Association Journal, March 1988.

Further information on data may be obtained from:
Division of Drug Control
RI Department of Health
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1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemia, familial periodic paralysis.

2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: **Hyperkalemia**—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS, and OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS and WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS and WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.

3. Correction of acidosis, if present, with intravenous sodium bicarbonate.

4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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Purification of Water for Drinking Purposes, with Special Consideration of Filtration of Micro-organisms

Gardner T. Swarts, MD

To obtain a pure water, the causes of impurity must be known in order to avoid them and to improve the quality of the water.

The various sources of water supply are:*

1. Rain water.
2. Surface water, including streams and lakes.
3. Ground water, including shallow wells and some springs.
4. Deep-seated water, including deep wells, artesian wells, and most springs.

Rain Water obtains its impurities from the air, the suspended atoms of dust, and gases which have arisen from the earth, from the accumulated dirt on roofs and in conductors; by storage in deep, uncleaned cisterns.

An attempt at purification may be made by filtering through layers of sand and charcoal, but this, it will be seen later, is hardly to be recommended.

Gardner T. Swarts, MD, (1857-1925), a recognized authority on dermatology, was secretary of the Rhode Island State Board of Health for 23 years until 1917.

In view of the current concerns about the state water supply, this paper, reprinted from the Transactions of the Rhode Island Medical Society, vol. 3, 1883-88, pp. 438-447, is relevant to today's health issues.

Rivers are liable to contamination from washing of the river banks which may be covered with refuse matter of barns and other out-buildings; from decaying vegetable matter on sides and bottoms of rivers; from manufactories and sewage of towns.

Nature purifies river water by oxydization, aided by agitation, deposition and dilution; this last probably plays the most important part in purification.

Ponds and Lakes. — Water from this source is apt to become turbid from lack of agitation, and from the growth of algae, to a certain extent also from surface washings of adjoining barn yards.

Surface Wells are liable to be contaminated from vaults and cesspools, and can be improved only by removing the cause of contamination.

Deep Wells, Bored or Artesian Wells are liable to contamination from the sub-soil lake, into which the well is bored, being used by manufactories as a receiver for refuse wastes which are injected into the sub-soil lake by an "absorbing well." Hardness is the principal fault of this source, and may be remedied by chemical treatment.

Springs may be considered as artesian wells established by nature.

Salt Water. — The only source of drinking water upon ocean steamers is improved by volatilization and condensation; the resulting insipid taste is remedied by charging with air before being used.

* Buck's Hygiene, p. 224.

Filtration — Nature's filter is the gravelly bed of a river from beneath which the water is pumped.

The more common method, as carried on in Berlin on a large scale, is to allow the water to percolate through the beds of large gravel, stones and sand, some ten feet in thickness, and by altering the use of the beds, the top layer of sand may be scraped off and replaced with new sand, or the old sand which has been washed (?) and exposed to the air. This, of course, acts as a strainer, and although the sand on top is removed, the same as we would remove the filtrate from a strainer, still the lower eight feet of cobble stones and gravel must necessarily become foul.

Filtration on a small scale, or Household Filtration. — This is the method of purification which appeals most directly to the satisfaction of the consumer, being under his control and offering something palpable to his senses of sight and taste, and suggesting to his imagination that something is being done as it ought to be done. The householder or tenant buys one of the various filters on the market, usually the one which is brought to him first. He places implicit confidence on the statement of the merchant who sells him the filter, that it will remove from water all organic and vegetable matters, as well as micro-organisms, especially those which produce disease, purify the water chemically, and decolorize it successfully, and the last agreement he demonstrates successfully by immediately placing the filter on the faucet supply and brings therefrom water as clear as a crystal, from water which before was highly colored and full of sediment. The other parts of the agreement he does not demonstrate, but leaves to the chemist and bacteriologist to prove whether or not the chemical purification and complete removal of organic matter has taken place, if they have sufficient interest to look into the matter; that interest, as a rule, being awakened only by the manufacturer of the filter presenting the chemist with a filter and a check, the results of the examination being usually in ratio to the amount of the check, and in favor of the filter.

Percy Frankland, Esq., has recently tested various filtering media to ascertain their ability to improve the water passing through, chemically, and bacteriologically. His experiments, conducted with due regard to sterilization, were as follows: Various materials, ground to the fineness that they could be passed through a sieve forty meshes to the inch, were placed in a glass tube drawn to a point, the tube being six inches

in height and one inch in diameter, protected at top and bottom with a layer of asbestos, and the whole sterilized three hours at 150°C. The water used for filtration was contaminated with urine in order to have a large number of micro-organisms to deal with; the water was analyzed before and after, with the result of little or no improvement found chemically, and, as will be seen by the following table, that bacteriologically, with most of the media upon first use, there was a large number of the micro-organisms removed, while after a month's use, most of them showed a decreased ability in this respect, with the exception of spongy iron and coke, which, even after four or five weeks, were still able to remove microbes successfully. It will be observed, however, that the rate of filtration was exceeding slow, the amount of water passing through being small, and hence the amount of retained filtrate within the meshes of the filtering media, corresponding small. Another series of experiments were also carried out by him to determine the effect of Clark's process for purifying water by agitating the same substances with the water to be tested, allowing them to settle, and then analyzing the supernatant medium of water.

Let us, for our own satisfaction, consider the subject of filtration.

Filtration is effected in three ways:

1. Straining.
2. Removal of suspended matters by adhesion to the sides of the interstices of the filtering media.
3. Substance within the interstices of the filter itself.

Successful filtration depending in all cases upon the size of the filter and the slowness with which the water passes through.

The chemical action of filtering media consists only of the oxygen which is held within the interstices of the medium, or in the meshes of its particles, as porous charcoal. The amount of oxygen may be considerable in proportion to the size of the filter, but is soon exhausted, not being replaced, but used up by the water passing through.

The mechanical action of filtration is the holding back of the particles of suspended matter which are too large to pass through the mesh of the strainer, whether that be felt, wire gauze, charcoal, sand, quarts or cotton. Such particles as are small enough to pass the first layer, which acts as a strainer, are entangled in the next layer, while a certain portion subsides upon the bottom of the interstices of the medium. This latter con-

dition is more marked in inverted filtration, *i.e.*, filtration from below upwards.

This last process has been illustrated by Wanklyn by taking two boxes of similar size, in one of which perforated shelves are introduced, and a water charged with carbonate of lime (the resulting precipitate from Clark's process) is passed through the box and allowed to settle.

In the box or tank without shelves, the precipitate is seen to settle first at the top, becoming more and more dense as we near the bottom, the sediment above finding resistance in the layer of the sediment next below, the resistance becoming greater near the bottom, which has received more than its proportion of sediment, as compared with the other layers above.

Now in the box with perforated shelves, this resistance is divided, and the sedimentation takes place more rapidly, the shelves serving to hold the mass of precipitate from accumulation on the layer next below it.

Wanklyn found that in boxes a foot square and 20 inches deep, with 24 plates of sheet zinc as shelves, it took eight hours for the water to clear in the box without shelves, and only 25 minutes in the box with shelves.

Now let us substitute our granules of quartz or charcoal, or our strands of felt, in place of the perforated shelves, and we have the same thing, only more subdivided and affording greater surface of resistance.

Again, the water which has passed through is seen to be clearer than the unfiltered water. The householder is satisfied, but are we? The question naturally arises, Where has the sediment gone to? It went in, it did not come out, hence it must be in the filter, and from the appearance of the unfiltered water it must be considerable in quantity. How much can the filter hold before the interstices of the medium are clogged up, and we find ourselves filtering through the accumulated filth? The manufacturer of the filter has also thought of this, and by various devices has endeavored to wash away the accumulated detritus from the strainer or the surface of the sieve (regarding the whole intercepting medium as a sieve). Others have gone further, and by reversing the filter, have the reverse current wash the detritus back and out, in some cases the water having first passed through a filtering medium, thus allowing the claim that they cleanse with filtered water.

It is evident that if the material to be filtered out can adhere so tenaciously to the particles of the filtering medium when the current is direct

and on "full head," that the same force of water, although coming in an opposite direction, will not be able to dislodge the organic or other matter which is so adherent, although much of the material lying loosely on the surface of the strainer, and some of the sedimentation with the interstices, may be successfully removed.

This is proven by the biological analysis of the water treated. For the chemical results of filtration I refer to the analysis made by Frankland, and as to the bacteriological, I have the opportunity of showing you the results of a series of experiments with all the various filters now on the market, which I was able to obtain. These were arranged in order upon the same line of pipe, at the Bacteriological Laboratory of Harvard Medical School, and hence the water used was the creamy Cochituate. A faucet was left on the same line of pipe with the filters, for drawing the water for the unfiltered analyses, and a faucet beyond that, to draw off any sediment which might accumulate, as is usually the case in a "dead end," however small the pipe.

Luther Filter. — Consists of a hollow metal ball, pierced at opposite points with inch holes and filled with a medium of packed charcoal. A brass screen of fine mesh an inlet and outlet. A modification of this filter consists of a felt diaphragm introduced in the centre of the charcoal. The tests following were made with the first mentioned form and should be considered as a direct current through animal charcoal. The filter is reversible and can thus be cleansed, being held in position by a cam lever place on one side.

Aborn Filter. — An advance upon the Luther filter. The water instead of passing in a straight stream, is deflected laterally around a metal diaphragm, extending through three-fourths of the centre of the globe. Thus the water courses through twice the distance of animal charcoal. A wire gauze — meshes to the inch, at inlet and outlet. This filter is reversible, and is easily opened by removal of a few screws, permitting of replacement of fresh charcoal.

Acorn Filter. — Consists of a hollow metal acorn about two inches in length and one and one-half inches in diameter at the base — having about a tablespoonful of animal charcoal as filtering medium — a screen at outlet and a plug of cotton at inlet prevent the displacement of charcoal by the stream of water. Is not reversible, and can only be cleansed by replacing the animal charcoal with a fresh supply, which is easily effected.

Gem Filter. — A metal cylinder one and one-half inches in length and two inches in diameter,

filled with small fragments of quartz or coarse sand. It has a gauze screen at both inlet and outlet, and is reversible, but the contents are not accessible and hence, cannot be removed.

Modifications in this filter consists of mixing the quartz with granular charcoal, and making the cylinder of glass.

Ideal Filter. — A small metal cylinder holding a horizontal diaphragm of felt one-fourth of an inch in thickness and one and one-half inches in diameter, supported on the underside by a metal diaphragm having numerous quarter-inch holes. It is cleansed by removing the felt, and replacing with a fresh disc.

Diamond Filter. — Is made of an iron filter case, the one used in tests being six inches in height and four inches in diameter, but they are made as large as 30×24. The filtering medium consists of a screen on a line with inlet at bottom, and one on line of outlet at top. The space between is filled with two layers of quartz, between which is placed a layer of animal charcoal, each layer being equal in thickness. A perpendicular metal partition divides the chamber into two compartments between the two screens. It is provided with a *four-way cock* at the supply end, two ways for inlet and two ways for outlet. When the lever on top of the four-way cock is parallel with the inlet, water will enter both chambers of the filter. For the purpose of cleansing, close the discharge faucet, and by turning the lever on the top of the four-way cock to the right, it will close the inlet in the left chamber and open the outlet. The water then passes up the right chamber and down the left and out of the open outlet (the waste) of the left. Then turn the lever to the left and the right chamber is cleansed by the same process; and by this means the filter is cleansed by filtered water.

The Howe filter consists of a metal cylinder — inches in height and — inches in diameter, having one inlet and two outlets, one for filtered water, and the other for the escape of the washings of the filtrate.

The filtering media consists of a perpendicular cylinder of felt, the inner surface of which rests upon a metal spiral core. In use the water enters from the supply, passes around the grooves of the spiral core, and forces through the felt diaphragm, and is drawn at the filtered water outlet. In cleansing, this last outlet is closed and the filtrate faucet opened, when the supply washes with great velocity around the spiral grooves, flushing them and the inner surface of the felt, escaping by the filtrate outlet.

It is claimed for this filter that it has a filtering area 160 times larger than at the $\frac{1}{2}$ inch inlet, which allows the water to filter 160 times as slow as a filter having a $\frac{1}{2}$ inch area.

A modification of this filter is made by substituting an unglazed porcelain diaphragm or cylinder in place of the felt.

It was intended to imitate as nearly as possible the conditions under which the filters would be used by the consumer.

All filters were tested at the same time and under the same conditions, as follows:

Water was drawn from the last faucet until it was evident that all air and detritus had been washed from the section of pipe upon which the filters were connected.

The first experiment consisted of drawing through the fillers about 4 Litres of water, in order to remove any dirt and dust which might be left in them, from packing and putting together.

About 50 c.c. of water was then drawn into a sterilized Erlenmeyer's flask having a sterilized cotton plug. One c.c. of the water was then taken from the flask with sterilized pipette, and mixed with 10 c.c. of sterilized nutrient, 10 per cent. gelatine (Koch's formula), and flowed upon a sterilized glass plate, which was placed upon a glass slab, under which was a jar of powdered ice, the whole protected with a sterilized bell jar, until the gelatine had hardened. This "plate culture" was then placed in a sterilized glass chamber with moisture, and allowed to remain for 48 to 72 hours, in a room with a temperature of 65° to 70°F., at the end of which time each individual microbe or micro-organism, which was introduced with the water into the gelatine by mixing, has grown for itself, by its own multiplication, an individual colony, subsisting upon the nutrient gelatine.

The number of these colonies was then counted with the aid of a lower power lens, a dark glass background and a measuring scale suspended over the plate culture.

In every detail, it will be observed, that the chance for introduction of micro-organisms, from the air, the hands and the utensils used, was reduced to a minimum, as is shown in the cultures where no colonies have formed.

The results obtained show that some, on the first use, successfully removed a certain proportion of the organisms from the water, while others, notably the Howe and Diamond, produced more colonies than there were in the unfiltered water. This may be explained by the fact that

Name of Filter				No. Colonies			
Howe, (felt diaphragm)	250	5	‡	4,876	1,260	71	Liq.
Luther	†	12	9,288	3,835	Liq.	204	14,240
Diamond	229	13	439	1,240	Liq.	475	72
Aborn	23	Liq.	2,088	3,564	30,132	94	1,120
Gem	15	15	10,106	5,673	117,000	2,125	‡
Acorn	45	36	†	12,530	Liq.	10,920	7,472
Ideal	19	21	2,100	627	1,000+	432	57,600
Unfiltered Aq.	24	26	27	13	58	36	70
Unfiltered water boiled 5 min.	2	5
Unfiltered water boiled 10 min.	0
Howe (porcelain)	§104+	28

* Sterilized approx. † All Liquified. ‡ Too numerous to be counted. § Not Sterilized.

All filters were cleansed after each use and allowed to stand unused, with the water supply shut off.

Before the 6th experiment, the filters were exposed to steam heat for one-half hour, and water drawn while still warm.

their filtering area is greater, and that they had arrested more organisms and had more to give up than the others. Furthermore, the others were never used before, while these two large ones had been. A test made 17 days later showed, in every case, a marked increase in the number of colonies in the filtered water, as compared with the unfiltered water. For instance, the unfiltered water contained 36 colonies of growth, while the filtered water showed the presence of colonies to the number of 2,000, 9,000, and 10,000. An examination made on the seventieth day, showed an increase in one instance, of 117,000.

The next experiment was to determine how far the consumer could cleanse his filter by sterilizing it in a simple manner. The filters were, on three or four successive days, exposed to steam heat for one-half hour, allowing the growth of such germs as might have survived the previous steaming, and had commenced again to multiply.

The result showed that, even with this precaution, in all instances the number of organisms in the filtered water exceeded the number in the unfiltered water to the extent of several thousand.

In conclusion I would say that the results of the experiments go to show conclusively that the organic matter which is retained in the meshes or interstices of the filtering media, contains organisms which feed upon the organic matter, and increase in numbers during the time that the

filter is, or is not, in use. That this is greatly increased in a position where heat is in proximity, as in a heated kitchen or beside hot water pipes.

It is not assumed that the ordinary bacteria of drinking water are injurious to health any more than albuminoid ammonia is injurious to health, but they indicate, by their presence, a large amount of organic matter, and it is upon this organic matter that bacteria of disease may find a lodgment and a fertile soil upon which to grow.

Typhoid fever and cholera are two diseases from which river water is liable to be contaminated by dejections. The micro-organisms producing these two diseases are propagated by the dejections, and are especially prolific in the presence of water; therefore, by analogy with the bacteria of drinking water, if one, only, of these disease germs finds its way into a filter, it has the opportunity of supplying the whole family with a considerable number of the specific germs at each drawing from the tap, while, had this individual microbe *not* been intercepted, he might have passed through the individual member of the household without doing harm.

It has been stated that no pathogenic micro-organisms are able to check the growth of, and destroy, pathogenic germs. This can only happen by destroying all of the nutrient material, but in a filter in use, the nutrition is constantly resupplied in the form of various kinds of animal and vegetable matters.

No. of experiment	1	2	3	4	5	6	7
Date of experiment	Dec. 10	Dec. 13	Dec. 27	Jan. 6, '87	Feb. 18	Mar. 7	
No. of days of use of filter	4000 c.c.						
Length of time which colonies had grown	0	3 days	17 days	27 days	70 days	*	
	8 days	3 days	5 days	5 days	3 days	4	

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PERIPATETICS

South County Hospital has recently appointed *Dr Nitin S. Damle*, a specialist in Internal Medicine, to its medical staff.

• • •

The Eighth Annual Veterans Administration Administrator's Hand and Heart Award, given annually to recognize an outstanding employee for exceptional sustained and compassionate direct patient care, was recently presented to *Dr Donald L'Europa*, Chief of the Acute and Initial Care Section of Ambulatory Care at the Providence VA Medical Center.

• • •

State Air Surgeon *Dr Blas Moreno* of the Department of Medicine at Memorial Hospital of Rhode Island, was honored at a retirement ceremony marking 27 years as an Air National Guard member.

• • •

The Memorial Hospital of Rhode Island in Pawtucket has appointed *Dr David C. Yoburn* to the active staff of its Nephrology Division.

• • •

Dr John B. Murphy, Chief of Gerontology at Memorial Hospital of Rhode Island, was part of a presentation on challenges of caring for aging parents at the Community Wellness Program sponsored by Memorial Hospital.

• • •

The American College of Radiology recently accredited Radiation Oncology Associates for three years. Staff at the radiation therapy center includes *Dr Banice Webber*, *Dr Roger Brotman*, and *Dr Anthony Yu*.

• • •

Dr Oswald R. Velis, cardiologist, and a member of the Kent County Medical Staff since 1964, has been elected to the Board of Trustees, Kent County Memorial Hospital.



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SEMI-ANNUAL CALENDAR OF CONTINUING MEDICAL EDUCATION EVENTS

NOTE: Lectures and courses are listed, when possible, by the date, sponsor, topic, speaker, and telephone number. Please call the contact number for additional information about the program.

BRADLEY HOSPITAL (401)434-3400 ext. 153

September
28 11:00-12:15 pm
Wednesdays Pine Room
Child Psychiatry Grand Rounds
Speakers to be announced

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(401)274-1100 ext. 1584 Obstetrics and Gynecology
Guest Lecturer or Lecture Series

(401)274-1100 ext. 1588 Obstetrics and Gynecology
Tumor Board Meeting
Every Tuesday 7:30 am
Speakers — Panel

(401)274-1100 ext. 1206 Perinatal Management Conference
Every Wednesday 7:45 am

(401)274-1100 ext. 1584 Obstetrics and Gynecology
Team Chiefs Rounds

YOCON® YOHIMBINE HCI

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L.) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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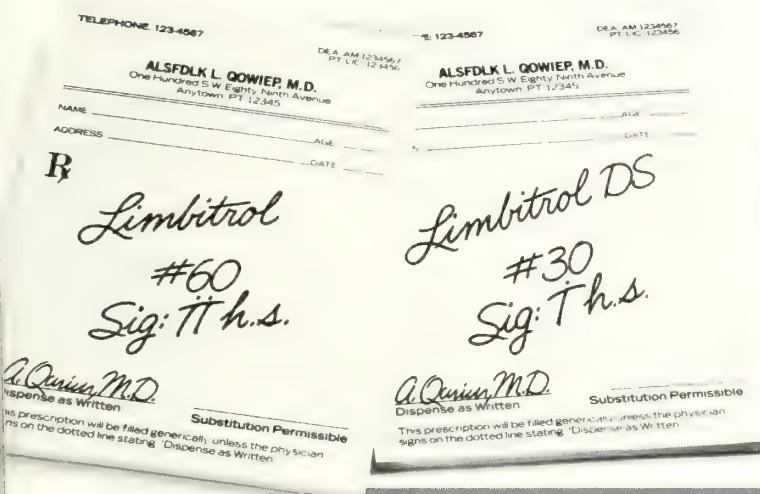
Every Monday/ Tuesday/ Friday	12:15 pm Medicine/Family Medicine Core Curriculum Conference Sayles #2 & 3 Conference Room Speakers to be announced
Every Tuesday	8:00 am Cardiology Conference Wood 6 Conference Room Richard A. Carleton, MD and colleagues
Last Tuesday of month	7:30 am Tumor Board Conference Physicians' Auditorium Manfred Steiner, MD and colleagues
Every Tuesday (except last Tues. of month)	8:00 am Hematology/Oncology Conference Immunology/Oncology Conference Room Manfred Steiner, MD and colleagues
Every Wednesday	8:00 am Pediatric Grand Rounds Physicians' Auditorium Louise S. Kiessling, MD and colleagues
Every Wednesday	10:00 am Medical Grand Rounds Physicians' Auditorium Guest speakers to be announced
Alternating Wednesdays	12:15 pm Pulmonary Case Review Sayles Conference Room #2 & 3 Frederic Hoppin, MD and colleagues
Alternating Wednesdays	Infectious Disease Conference Sayles Conference Room #2 & 3 Kenneth H. Mayer, MD and colleagues
Every Thursday	8:00 am Orthopedic Conference Sayles Conference Room #2 Richard G. Bertini, MD and colleagues
Every Thursday	8:00 am Surgical Grand Rounds Physicians' Auditorium Stephen J. Hoye, MD and colleagues
Every Thursday	12:15 pm Family Practice Grand Rounds Physicians' Auditorium Vincent R. Hunt, MD and colleagues

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July 14	Case Conference Saul Martin, MD — Presenting David Kroessler, MD — Moderating
28	Case Conference John Melchionna, MD — Presenting Richard Goldberg, MD — Moderating
August 11	Case Conference Nina Nizetic, MD — Presenting M. Eileen McNamara, MD — Moderating
25	Case Conference Christopher Joo, MD — Presenting Leah Cullen, MD — Moderating
September 8	Case Conference Lorin Mimless, MD — Presenting Duane Bishop, MD — Moderating
22	Case Conference Frank Jones, MD — Presenting Richard Goldberg, MD — Moderating
October 6	Case Conference Ronald M. Stewart, MD — Presenting M. Eileen McNamara, MD — Moderating
20	Case Conference Constantine Loures, MD — Presenting Matthew Edlund, MD — Moderating
November 3	Case Conference Aimee Schwartz, MD — Presenting Leah Cullen, MD — Moderating
17	Case Conference Sarah Zamri, MD — Presenting Duane Bishop, MD — Moderating
December 1	Case Conference James McGuire, MD — Presenting M. Eileen McNamara, MD — Moderating
15	Case Conference Max Faintych, MD — Presenting Matthew Edlund, MD — Moderating
29	Case Conference Saul Martin, MD — Presenting Duane Bishop, MD — Moderating

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References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Feighner VP, et al: Psychopharmacology 61:217-225, Mar 22, 1979.

Limbitrol® @

Tranquilizer-Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants; concomitant use with MAOIs or within 14 days of monoamine oxidase inhibitors (then initiate cautiously, gradually increasing dosage until optimal response is achieved); during acute recovery phase following myocardial infarction.

Warnings: Use with caution in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur when used with anticholinergics. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia, prolongation of conduction time, myocardial infarction and stroke reported with tricyclic antidepressants, especially in high doses. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs: **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. **Neurologic:** Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extra-pyramidal symptoms, syncope, changes in EEG patterns. **Anticholinergic:** Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. **Allergic:** Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus. **Hematologic:** Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. **Endocrine:** Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Overdosage: Immediately hospitalize patient. Treat symptomatically and supportively. I.V. administration of 1 to 3 mg physostigmine salicylate may reverse symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

How Supplied: Double strength (DS) Tablets, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and Tablets, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.



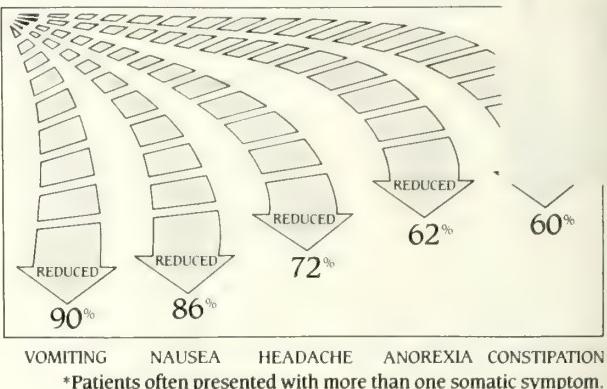
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Caution patients about the combined effects of Limbitrol with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car. In general, limit dosage to the lowest effective amount in elderly patients.

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*Patients often presented with more than one somatic symptom.

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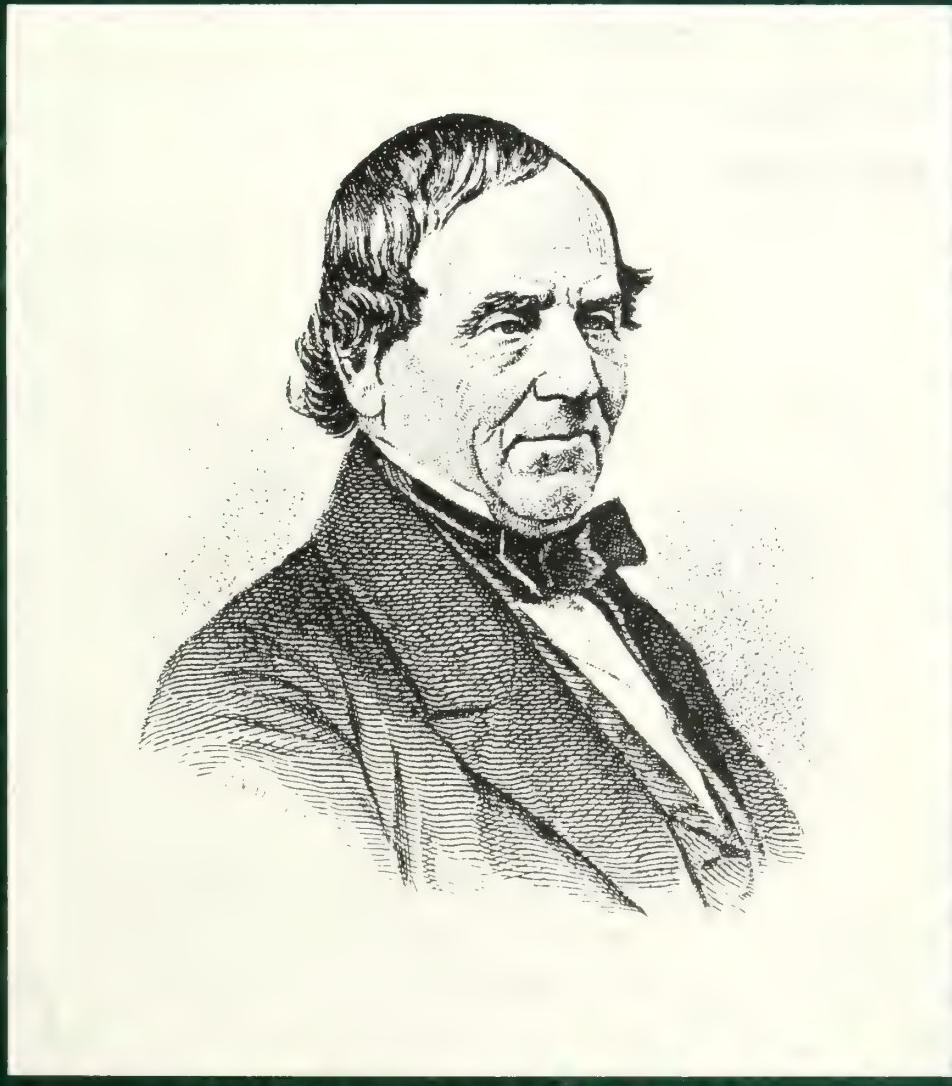
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Volume 71, Number 8



USHER PARSONS, MD

1788-1868

(See page 321)

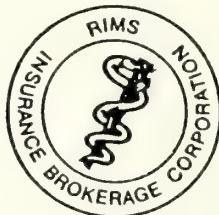
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**ROSALYN P. STERLING-SCOTT, M.D.**

Assistant Professor of Surgery, UCLA School of Medicine and Drew University of Medicine and Science, Los Angeles

Associate Surgeon, Department of Cardiovascular & Thoracic Surgery, Centinela Hospital Medical Center, Los Angeles

Major, U.S. Army Reserve

EDUCATION Rensselaer Polytechnic Institute, Troy, NY, B.S. Chemistry; NYU School of Medicine, New York, M.D.

RESIDENCY Boston University School of Medicine (Cardiovascular); Saint Vincent's and St. Claire's Hospitals, New York City (General Surgery)

FELLOWSHIP First Mary A. Fraley Cardiovascular Surgical Research Fellow at the Texas Heart Institute, Houston

OUTSTANDING ACHIEVEMENTS Author of numerous articles, including "Indications for Early Bypass Grafting Following Intracoronary Streptokinase"; author of "The Female Surgeon—Dawn of a New Era" chapter in *A Century of Black Surgeons—The U.S.A. Experience*; Board of Directors, Association of Black Cardiologists; Secretary, Drew Society

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Brief Summary. Consult the package insert for prescribing information.

Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

Axid is indicated for maintenance therapy for duodenal ulcer patients, at a reduced dosage of 150 mg 1 s. after healing of an active duodenal ulcer. The consequences of continuous therapy with Axid for longer than one year are not known.

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H₂-receptor antagonists.

Precautions: General—1 Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2 Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3 Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for uricobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions—No interactions have been observed between Axid and theophylline, chlordeoxiprole, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high dose males compared to placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement.

compared to concurrent controls, and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive, and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery is not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, and the mouse lymphoma assay.

In a two-generation, parental and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose, and in Dutch Belted rabbits at doses up to 55 times the human dose, revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydronephrosis, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Nizatidine is secreted and concentrated in the milk of lactating mothers. Pups reared by treated lactating rats had depressed growth rates. Although no studies have been conducted in lactating women, nizatidine is assumed to be secreted in human milk, and caution should be exercised when nizatidine is administered to nursing mothers.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among the more common adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs <0.1%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported. It was not possible to

determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L); and in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic—Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H₂-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs.

Intestinal—Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients. Rash and exfoliative dermatitis were also reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported.

Overdosage: There is little clinical experience with overdosage of Axid in humans. If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous LD₅₀ values in the rat and mouse were 301 mg/kg and 232 mg/kg respectively.

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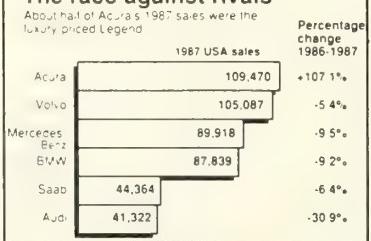
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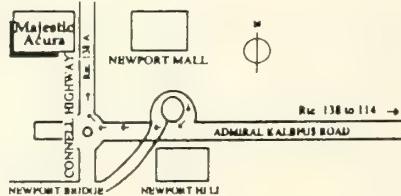
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... a 65-year-old white male with adenocarcinoma of the lung, aphasia and right arm weakness

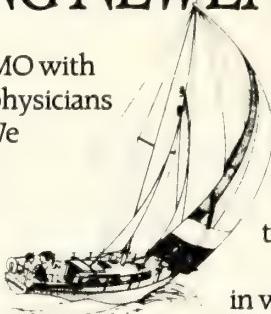
Tom J. Wachtel, MD

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EDITORIALS

New Opportunities for Physicians to Provide Smoking Cessation Interventions to Their Patients

Three recently published reports about cigarette smoking are likely to be of interest to members of the Rhode Island Medical Society. They each provide physicians with new opportunities to help their patients stop smoking. On May 16, 1988 the United States Surgeon General published *Nicotine Addiction*, the latest in a series of reports on The Health Consequences of Smoking.¹ The report, which received extensive press coverage, documents the extensive scientific evidence which establishes that nicotine is the psychoactive drug in tobacco that causes dependence and addiction. The report also draws close parallels between nicotine and other drugs that cause addiction, such as heroin and cocaine and reviews the treatment of tobacco dependence. As noted in the report's preface, written by C. Everett Koop, MD, ScD, Surgeon General of the United States, the report has many public health implications, many of which apply to practicing physicians.

Physicians should be aware of the addictive nature of smoking and other forms of tobacco use and the treatment available to those who want to stop. The release of the report and the media coverage which it has received provide physicians with an opportunity to discuss smoking with their patients. This "teachable moment" may be utilized to explore smokers' feelings about smoking, their desire to quit, and their thoughts about how to go about quitting. Many patients feel guilty about not being able to give up smoking and may have become demoralized as a result of repeated failures. Physicians can help to absolve patients' guilt by pointing out that they are innocent victims of the addictive properties of nicotine. It is very important not to blame patients for being addicted, for they became "hooked" before the addictive properties were well known. At the same

time, offering empathy and understanding about the difficulty they may have had in quitting may increase their motivation to try smoking cessation again. Providing direct support by offering help with the withdrawal process may also increase their willingness to try. If there is evidence from their smoking history of significant tobacco dependence (ie, a history of repeated failures, significant withdrawal symptoms upon cessation, smoking the first cigarette of the day shortly after arising), treatment with nicotine gum or referral to a formal treatment program may be considered. Effective smoking cessation counseling strategies that can be provided by physicians are described in more detail in recent reports.^{2,3}

The effectiveness of physician-delivered smoking cessation interventions is the subject of several papers in the May 20, 1988 issue of the *Journal of the American Medical Association* (JAMA). The United States Preventive Services Task Force, after an extensive review of published controlled trials of smoking cessation interventions in medical practice, published their recommendation for smoking cessation counseling.⁴ The recommendation of this blue-ribbon panel of experts on prevention and primary medical care states, "To improve smoking cessation rates, patients should be exposed to a variety of intervention techniques on multiple occasions, delivered by both physicians and nonphysicians." They base this recommendation on the results of a meta-analysis of 39 controlled trials which demonstrated 5.8 per cent higher one year smoking cessation rates for patients who received smoking cessation counseling than for controls. The Task Force also cited evidence which suggests that direct face-to-face advice, scheduled "support visits" or follow-up telephone calls, and nicotine gum (when

coupled with other interventions) all increase effectiveness. Use of self-help materials and referral to community programs were also recommended.

Ronald M. Davis MD, Director of the Office on Smoking and Health, Centers for Disease Control, wrote an editorial in the same issue of JAMA calling for a coordinated national strategy to unite physicians against smoking.⁵ Davis cites evidence which suggests that physicians as a group are not doing all that they can do to encourage cessation among patients who smoke. Data from recent surveys reveal that only 45 per cent of smokers report that a physician had ever advised them to quit.^{5,6} He encourages physicians to utilize materials that have been developed to aid them to develop effective smoking cessation strategies and lists resources currently available. He also urges cooperation of medical societies, voluntary health organizations, and public health organizations in coordinating the efforts of physicians in the campaign for a smoke-free society.

Finally, in the same issue of JAMA, Glassman and colleagues present new evidence that clonidine, an alpha₂-noradrenergic agonist, is effective as a smoking cessation intervention.⁷ Clonidine has previously been shown to be effective in diminishing withdrawal from opiates and alcohol⁷ and, in an earlier study by Glassman and colleagues, effectively reduced withdrawal symptoms in subjects who were abstinent from cigarettes for 24 hours.⁸ If subsequent studies confirm clonidine's effectiveness as an aid to smoking cessation, it will increase the number of possible interventions that physicians can utilize to help their patients stop smoking and further enhance the role of the physician in smoking cessation efforts. The cooperation of the medical profession is urgently needed.

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Early Referral to Ophthalmologist and Close Monitoring Are Key to Preservation of Eyesight for Diabetics

Diabetic retinopathy is the leading cause of blindness in the United States for persons between the ages of 20 and 60. Diabetes accounted for one per cent of cases of blindness 50 years ago. Today it is responsible for 18 per cent of blindness in the United States. The discovery of insulin in 1921, along with improved medical care in general, has greatly improved the quality of life for people with diabetes and has significantly increased their lifespan. But along with the improvement in quality and length of life has come the late complications of diabetes, including diabetic retinopathy.

In 1976 a landmark publication gave new hope to the millions of patients with diabetes who were fearful of losing their eyesight from their disease. The Diabetic Retinopathy Study, a collaborative effort involving 23 medical centers coordinated by the National Institutes of Health, reported that treatment of proliferative diabetic retinopathy reduced the risk of severe visual loss by 50 per cent.

Three years later, a study revealed that 65 per cent of primary care practitioners did not know that LASER treatment was available for their patients with diabetes! Fortunately, the media have popularized such miracles of modern medicine, and most patients today are aware that LASER eye surgery is offered in Rhode Island.

I wonder how many physicians twelve years after the Diabetic Retinopathy Study are aware that their patients with diabetes may benefit from LASER treatment *before their vision fails*. The latest published report by the research group on diabetic retinopathy has now clearly demonstrated the effectiveness of LASER photocoag-

ulation in an early and very common form of diabetic retinopathy called "macular edema." This can be present (and successfully treated) in a diabetic patient's eye *before sight is lost!* And it has been shown to reduce the risk of severe visual loss by 50 per cent.

Thus, we who are concerned professionally with the preservation of sight are anxious to disseminate the message to the general medical community that we can now help diabetics preserve their eyesight! *If we see the patients early enough in the course of their disease.* The National Diabetes Advisory Board recommends that referral to an ophthalmologist be made for Type I diabetics present for five years, and for Type II diabetics when the diagnosis is made.

Early identification and close ophthalmic monitoring of retinopathy is the key to successful preservation of visual acuity in a diabetic patient. Thus the optimal time for the most effective application of LASER therapy may be recognized. Please help!

Stephen J. Richman, MD, FACS, President,
American Diabetes Association
Rhode Island Affiliate

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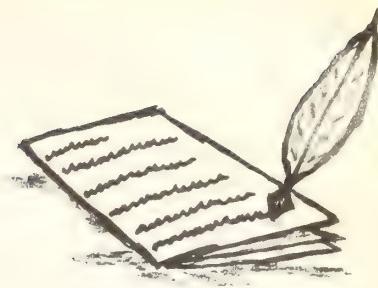
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EDITOR'S MAILBOX



AIDS Legislation

To the Editor:

I am dismayed by several aspects of the recent editorial on AIDS testing and the proposed legislation (RIMJ v. 71, p. 171, May 1988). First, while this bill is comprehensive as well as controversial, the editor's reasons for blanket endorsement are only briefly given. I do think a more detailed explanation of the reasons for the editor's support is indicated. Second, the editor implies that opposition to the bill represents special interest groups. While I do not share many of the views of the opponents, they believe they are representing the public's good as much as the editor appears to believe he is doing in writing an editorial for the local medical society journal. The current controversy necessitates that we maintain an open mind and communication between different groups in order to develop a consensus for control of the current epidemic. Accusations about short-sided views and naive arguments are not likely to serve this purpose. Third, in concluding the editorial by stating that "we strongly support," to whom is the editor referring? Does "we" indicate an unanimous view of the editorial board of the RIMJ? To what extent does the editorial board represent the opinions of the Medical Society? Fourth, the editorial implies that this legislation is not only essential but progressive. I hope the editor realizes that some who have been extremely involved in the AIDS epidemic, such as members of the Governor's AIDS Task Force, oppose the bill on the very grounds that it not only is non-essential but also is regressive and discriminatory legislation.

I write this letter not so much as to criticize or support the bill, but rather to indicate the complexities of these issues and resulting need to give detailed thought and discussion. We need to respect those who may not agree with our views. I in no way want to distract from the editor's considerable contributions to the Medical Society in editing the journal these many years and hope that the editor will consider these criticisms as constructive.

Georges Peter, MD
Director, Division of Infectious Diseases
Rhode Island Hospital
Professor of Pediatrics
Brown University

Since the Editorial was written, the bill, without the controversial housing amendments, has been passed by the General Assembly and will be signed by the Governor. The Rhode Island Medical Society supported the legislation. The Editorial "we" embraced both the Society and the Editor. —Ed.

Commentary on Off-Site Day Care at IMH

To the Editor:

As Chief Executive Officer of the Institute of Mental Health (IMH), I write to comment on your publication of an article titled "Off-Site Day Care at the Institute of Mental Health 1982-1987" which appeared in the May 1988 edition of the *Rhode Island Medical Journal*.

First of all, let me say that I am perplexed that your journal should publish such an article without some effort to verify the points made therein. The article is devoid of any factual content regarding benefits of the IMH Off-Site Day Program to patients. Furthermore, it makes a number of rather serious allegations regarding detrimental effects of the program to patients, discharged patients sleeping in alleys, begging food, committing crimes, being exploited and dying without even anecdotal support. There is no factual information supporting the views of the author or the author's unfounded allegations regarding the motivations — ie, to keep the numbers up, to put the perpetuation of the program above patient care, and generally to ignore the

welfare of the patients in order to achieve cosmetic administrative goals. The paper is a combination of misperception, bias, and misinterpretation of facts and events. In particular, on behalf of the patients and the staff, I would address those points which misrepresent their circumstances.

It is true that the number of patients who show the most immediate benefit from programs such as the off-site program have been reduced in number at the IMH. The Institute of Mental Health has without doubt the most difficult-to-treat psychiatric population in the State of Rhode Island. Approximately 100 of the patients at the IMH have a length of stay exceeding two years. Many of these patients have been at the IMH in excess of five years. Despite the severity of their problem and at times seeming ineffectiveness of treatment, it is nonetheless the responsibility of the IMH to provide care and treatment for all of its patients. For many of the patients for whom I speak, their long residence in the institution in and of itself has had detrimental effects. These effects are manifest in their social isolation and in a wide range of deficiencies in the skills necessary for every-day living. It is the philosophy of the IMH that there are two important aspects of the care and treatment that needs to be provided for these patients. First, psychiatric symptoms need to be brought under control and, if possible, be maintained in permanent remission. Achievement of this goal does not necessarily imply that a patient is ready for discharge. The second goal of treatment has to be to prepare the patient for living in the community through the development of at least a basic set of functional life skills. It is further the philosophy of the IMH that contact with the community and a change of venue, so to speak, are beneficial to patients in later process. It is for this reason that outside programming was developed at the IMH and that it continues. Attendance at off-site programs in and of itself seemed to be of more benefit than remaining on inpatient wards. It is for this reason that even difficult patients who show only minimal or at times no progress are included in the off-site program.

I should also like to point out that the "Administration" of which Mr Anez complains is the Clinical Administration of the IMH. This group is composed of two psychiatrists each with more than twenty years' experience in the treatment of patients with long-term and debilitating mental illnesses, two PhD Clinical Psychologists, two MSW Social Workers, a master's level psycholo-

gist, and a master's level Rehabilitation Counselor. While it may be possible that a bachelor's level social worker has more knowledge and expertise in the treatment and rehabilitation of psychiatric patients than the combined education and experience of the Clinical Administrative group, one would think, however, that some evidence of this would be required before accepting it as the representative view of a facility and its programs.

In conclusion, I would like again to express my surprise that your journal should print an article such as this full of spurious allegations and accusations of unworthy motivations on the part of the Administration of the IMH without some factual evidence or at least study of the issue.

David E. Askew, PhD
Hospital Clinical Administrative Officer
Institute of Mental Health
Rhode Island Department of Mental Health,
Retardation, and Hospitals

We shall be pleased to publish a paper on the end results of the program. — Ed.

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Annual Meeting of the Rhode Island Medical Society House of Delegates

Summary of Minutes

On May 6, 1988, the House of Delegates, of the Rhode Island Medical Society held its Annual Meeting. The following is a summary of actions taken.

- (a) Elected officers and committee members as reported by the Nominating Committee.
- (b) approved the recommendation of the Council that Rhode Island Medical Society Bylaws be amended in the following sections:
 - Standing Committee
 - Occupational Health and Environment
 - Mediation Committee
 - Public Laws Committee
 - Quality Assessment Committee
- (c) accepted a resolution from Rhode Island Medical Society Council making Norman A. Baxter, PhD, an honorary member of the Rhode Island Medical Society.

RHODE ISLAND MEDICAL SOCIETY BYLAWS

It was the recommendation of the House of Delegates to the general membership that Rhode Island Medical Society Bylaws be amended as follows (new phraseology in the bylaws is underscored):

Amendment:

- 8.1 Names of Standing Committees and Election of Committee Members. The standing committees of the Society, of which the President and Secretary shall be ex officio members, shall include in alphabetical order: Impaired Physician, Liaison, Mediation, Medical Economics, Occupational Health and Environment, Peer

Review Committee on Physician Competency, Public Laws, Publications, Standards and Credentials, Trustees of the Caleb Fiske Fund, and Trustees of Special Funds. Except as noted below, committee chairperson and members shall be elected by the House of Delegates at its annual meeting for one-year terms. They shall assume office at the close of the annual meeting of the Society and shall serve until the next annual meeting. The nomination process for committee chairmen and members shall be the same as described in Section 3.1. All committee members elected by the House shall be members in good standing of RIMS. In the event of a vacancy on any committee, the President, with the advice and consent of the Council, shall appoint a member to complete the unexpired term.

Amendment:

- 8.1(5) Mediation. The Committee on Mediation shall consist of nine members and a chairperson, each of whom is elected annually by the House of Delegates. Members may serve a maximum of ten years.

The committee shall review complaints referred to it concerning the professional conduct of RI Physicians.

The committee shall have the authority to require the attendance of any member to answer allegations of unprofessional conduct, upon at least seven days written notice to the

member. Failure of the member to appear before the committee without justifiable cause shall be reported to the Council for disciplinary action.

The committee, after investigation, shall have the authority to refer charges of unethical or unprofessional conduct against a member to the Council.

Amendment:

8.1(7) Occupational Health and Environment. The Committee on Occupational Health and Environment shall consist of nine members elected by the House of Delegates. The Committee shall keep itself informed concerning: (1) conditions and practices that affect or potentially affect the health and well-being of our citizens in homes, schools, workplaces, and in other settings; (2) the medical care rendered to our citizens as a result of occupational and environmental hazards; (3) legislation relating to occupational health and safety and environmental hazards. The committee shall also advocate such measures as in its judgment will improve the welfare of employees and reduce risks posed to the populace by environmental conditions.

Amendment:

8.1(9) Public Laws. The Committee on Public Laws including its chairperson, shall be appointed annually by the President. Its membership shall include representatives of those specialty societies and others whose interests and concerns are, in the judgment of the President, most likely to be affected by existing or proposed legislation. The Committee shall review such legislation in light of the Society's policies and recommend appropriate positions to the President to assist in fulfillment of his or her role as public spokesperson for the Society 3.3(4). In the absence of a stated policy, the committee shall recommend a policy position to the Council for adoption.

Deletion:

8.1(1) Annual Meeting and Awards Committee

Deletion:

8.1(4) The Library Committee

Deletion:

8.1(11) Quality Assessment Committee

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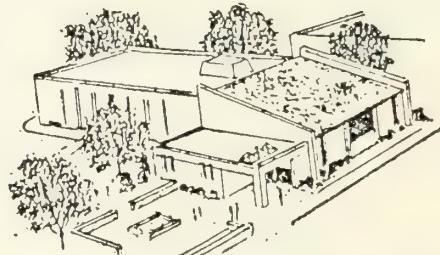
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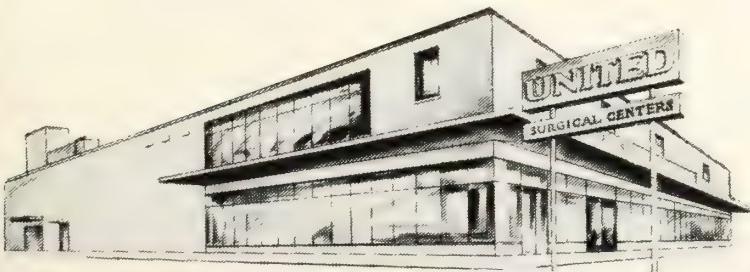
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PRESIDENTIAL ADDRESS

Richard G. Bertini, MD

One evening 43 years ago, my dad and Doctor Jessie P. Eddy, III snuck a teenage boy into the old operating room at Memorial Hospital in Pawtucket to see an emergency case. I've been hooked ever since. I'm glad I chose to be a doctor. I'm proud of our profession, and I'm proud of our Medical Society.

I'm here today to tell you that the Rhode Island Medical Society (RIMS) is an exciting, progressive, growing, innovative, proactive, public spirited association — a Medical Society on the way up, and not yet arrived, with real depth of purpose. Since 1812 the Rhode Island Medical Society has worked hard to insure that people receive the best medical care. So much has happened in the past year that I'll just touch the highlights.

Membership continues to soar. We now officially represent 1500 of the 1900 doctors in active practice in Rhode Island. We received 118 new members last year.

Public Relations

Our relationship with the print and broadcast media is good. *The Providence Journal* has been pro medicine with lead editorials praising our position on AIDS and other issues. Letters to the editor from the RIMS president almost invariably occupy the key top-left spot on the editorial page. Favorable articles have appeared frequently in the *Journal* and the *Pawtucket Evening Times* (my hometown paper). Reporters and journalists frequently telephone the Medical Society for background material and our opinion.

Read at the 177th Annual Meeting of the Rhode Island Medical Society, May 6, 1988.

There have been numerous telephone radio interviews with stations in Providence and Newport. Television coverage has been good, with numerous opportunities to present our case via this medium. I have been treated fairly and with a certain deference. Even a panel with ultra-liberal United States Representative Barney Frank of Massachusetts was a positive experience. The most recent television media event followed a demonstration by irate midwives at our Medical Society building.

We are blessed with a superb staff and have excellent in-house public relations expertise. The importance of media training for the RIMS president, who is the elected spokesperson for the Society, cannot be over-emphasized. Especially with television, there are simple yet valuable techniques that can be used to advantage.

Legislation

It seems as if the State House is my second home. Mark Montella and I have testified on many bills, some of which have been authored by the Medical Society, and our score is pretty good. Let me list them in some detail, because I think that society's perceptions and expectations about medical matters are best seen through the legislative process. Here they are: fetal alcohol syndrome, mandatory assignment (which eliminates direct billing of fees), physicians' records, obstetrics (requiring yearly statistical analysis of each practice in pamphlet form), patient notification by doctor by mail if the doctor discontinues participation in an insurance plan, prohibiting fees for medical reports to attorneys.

The politics of acquired immunodeficiency syndrome (AIDS) is intriguing and still in flux. How grateful we should be to our Medical Society

AIDS Advisory Committee for its rational approach to the AIDS pandemic. The real culprits here are fear and lack of knowledge. We should do all we can to protect the civil liberties of those who test positive for human immunodeficiency virus (HIV).

Durable Power of Attorney for Health Care (supported by RIMS) was adopted by the General Assembly late in the last session.

Other proposed legislation gives more independence or change in reimbursement patterns to nurse practitioners, physical therapists, physician assistants, and midwives.

The midwife issue is particularly rancorous. Recent editions of *The Providence Sunday Journal Bulletin* carried a perceptive article by the chief editorial writer, which read as follows:

It seems that much of the enthusiasm for midwifery and home birth is really antagonism to the medical profession. People are not required to venerate their doctors, but who could seriously believe that the medical technology of obstetrics and gynecology is somehow designed to subjugate women? . . . Most doctors are practitioners of the healing art and dedicated people. But it remains largely true that, in a single generation, the image of the MD has radically changed. . . . From the kindly general practitioner . . . , doctors are now seen as Ivan Boeskys' in white — rushed unsympathetic, squeezing every penny from a multitude of customers. Physicians are respected, but not beloved. . . . That is the doctor's dilemma — the quality of medicine has largely superseded the quality of care . . . to the degree that the profession spawns a corporate style, as physicians grow remote from their suffering clientele, a vacuum is created that somehow will be filled.

It couldn't be better said. Patients deserve, and in many subtle and not-so-subtle ways, are demanding art as well as science from us. The proposed legislation dealing with the allied health care professionals is a symptom of that patient yearning.

On a different level, these legislative proposals can be viewed as an assault on the MD degree. Our agenda is to unite all doctors (private-practice, full time, employed, academic) within the Medical Society.

The Malpractice Crisis

There were three forums or debates on perspectives in the malpractice crisis: One with State

Representative Jeffrey Teitz, chairman of House Judiciary, sponsored by the Charles Evans Hughes Society at Brown University; another with attorneys Thomas Gidley and Leonard Decof and State Senator David Carlin, sponsored by the Department of Family Medicine at Memorial Hospital in Pawtucket; and a third with attorney/physician Harvey Waxman of New York City, Doctors Milton Hamolsky and Kenneth Liffman and hospital attorney John Dolan, sponsored by the Department of Surgery at Rhode Island Hospital. These three events gave us a chance publicly to articulate the concept of the new social ethic — an ethic that calls for compensation for medical misadventures regardless of fault.

Society is telling us that they want to be paid for bad results, regardless of the cause, regardless of whether there is really negligence involved, regardless of whether the doctor seemed to be a nice person or a nasty one. That is the new social ethic, and that kind of support for injured people is an admirable social goal. But it is patently poor social policy to force 1900 Rhode Island doctors to fund what is essentially a social welfare entitlement system a million Rhode Islanders can tap into.

Our inability to resolve the liability crisis is our biggest failure. The request for a 50.8 per cent increase by the Medical Malpractice Joint Underwriting Association (MMJUA) is devastating evidence of the growing crisis in Rhode Island. Our worst fears are being realized and, unless creative solutions are forthcoming, the crisis will continually deepen. The fact that more money is spent determining fault than in compensating the injured is *prima facie* evidence of a fault in the current legal system. Three legislative proposals introduced by the Rhode Island Tort Reform Coalition would be of some help: modification of joint and several liability, certificate of merit, and change in the statute of limitations.

Innovative pilot programs are ideally suited for a state of our size. We desperately need creative experimentation. Some suggestions for alternative dispute resolution are arbitration, the double-blind approach of Jeffrey O'Connell of the University of Virginia Law Faculty, the American Medical Association (AMA) administrative fault-based proposal, and a compensation pool.

So much time, energy, and talent are wasted in coping with the insurance liability mess, that it is demoralizing for our members and harmful for the public. We shall see more and more fallout as doctors elect early retirement or modify

practice patterns. Access to good-quality medical care is becoming more and more difficult. No wonder the stress management symposium sponsored by the Providence Medical Association was such a smashing success.

Miscellaneous

At last we are flexing our economic muscle. The energizing of the Rhode Island Medical Political Action Committee (RIMPAC) and the activation of the RIMS Insurance Brokerage Corporation (IBC) bode well for the future.

Our relationships with the movers and shakers — the Hospital Association of Rhode Island (HARI), the Health Department, Blue Cross and Blue Shield (BC/BS), elected officials, community leaders — continue to improve. RIMS is perceived as the authority in medical matters, and our advice is constantly sought.

This year the Charles V. Chapin Oration was separated from the annual meeting and given in a hospital setting guaranteeing its success. Doctor Robert Gallo, this year's Chapin Orator, spoke to an overflowing crowd of 500 at the new Sayles Conference Center at Memorial Hospital in Pawtucket. Modifying the requirements for the Caleb Fiske Prize Award gives the Medical Society flexibility in making that award. We have made a firm commitment to continue to administer Continuing Medical Education (CME) credits. Recent bylaw changes make us more contemporary. The charge of the Occupational Health Committee is expanded to include environmental concerns. The Search Committee, ably led by Peter King, and assisted by the New York based firm Korn/Ferry International, wisely chose our own Newell Warde to succeed Norman Baxter as Executive Director.

The crown jewel of the Medical Society is our peer review system. Our experienced committees on Competency (unique to this Society), Mediation, and Impairment offer effective and confidential help to physicians and the public. We all owe the 45 dedicated individuals who make up these committees our thanks.

A landmark event was the completion of negotiations and formal transfer of our library to Brown University. Brown acquired 50,000 volumes. Nine thousand are now housed in the rare-book collection at the John Hay Library. All RIMS members have full access to the Brown Library system. We do well by doing good. Plans for our building in the space freed up by the Library transfer are on hold until the neighboring Capitol City Project is further clarified.

After four years of work, a Code of Professional Responsibility has been approved jointly by RIMS and the Rhode Island Bar Association.

I feel like a J. Paul Getty, who, when asked how much money one needed to retire, replied: "Just a little bit more." How often I've wished for just a little bit more time and energy and talent to do the president's job right.

Like a miser, I'm going to hoard all the wonderful memories of this busy year. The support of our members has been wonderful — particularly that of the past presidents — those veterans of this trial by fire. I even savor the letter from a friend calling me "Dr Milktoast" for not walking out of that famous Division of Business Regulation (DBR) hearing in May 1987, and the anonymous typewritten note castigating our cooperation with United States Senator Claiborne Pell for offering help to the Afghan wounded.

In twelve years we shall celebrate the dawn of a new century and the new millennium. It can be a time of unparalleled progress, technological achievement, and wellbeing; or it could be a time of unbridled destruction.

For medicine, my guess is that the two great issues of today will have become irrelevant. A vaccine or at least an effective treatment for AIDS will have been developed. The liability crisis, having become so bad, will have been resolved. My guess is that the major concerns of doctors will be the preservation of the physician control of decision making in the care of the sick and the new ethic of medicine — the right to live, the right to die.

I hope we shall all be there then to engage in that dialogue.

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. . . a 65-year-old white male with adenocarcinoma of the lung, aphasia and right arm weakness

Tom J. Wachtel, MD

Presentation: Joan Teno, MD, Department of Medicine, Rhode Island Hospital

A 65-year-old right-handed white male with adenocarcinoma of the lung and status post left pneumonectomy was admitted to Rhode Island Hospital with a 48-hour history of difficulty in speaking and right arm weakness.

Two years prior to admission a nodule was found on chest x-ray film for which he underwent a left lung pneumonectomy for moderately well-differentiated peripheral adenocarcinoma with negative hilar nodes. Two months prior to admission the patient developed back pain attributed to a destructive lesion of the third lumbar vertebra, which was treated with radiation therapy. One week prior to admission the patient developed left leg numbness and weakness. A computed tomography (CT) scan of the head showed a low-density lesion in the right parietal area. The patient was placed on dexamethasone, 4 mg four times daily with resolution of the weakness. Forty-eight hours prior to admission the patient's wife noted that he was having difficulty finding words and also right arm weakness, which progressed. At admission the patient was able to speak only one word at a time and developed complete paralysis of his right hand and arm. He could understand and follow simple commands. He did not complain of headache, photophobia, fever, chills, difficulty walking, or stiff neck.

On physical examination, the patient had the appearance of a middle aged male, restless yet alert, and oriented to person, place, and time. The blood pressure was 150/90, respirations 16, pulse 80, and temperature 96°F. The pupils were equal, round, and reactive, and fundi were unremarkable. Examination of the oropharynx, nose, and tympanic membranes was normal. The lungs revealed decreased breath sounds on the left, with the right lung clear to auscultation and percussion. The heart sounds were normal without murmur, rub, or gallop. The abdomen was soft, nontender, and without hepatosplenomegaly. Upon neurologic examination the patient was alert and oriented. He was unable to spell his name, but could repeat three letters forward and backward. He had difficulty with simple calculations, was able to read, and could comprehend and follow simple commands. He spoke in simple sentences only. Cranial nerves 2 to 12 were intact. The motor examination showed paralysis of the right hand and wrist ($\frac{1}{2}$). The left hip flexors were $\frac{1}{2}$. Deep tendon reflexes were normal except the right biceps, triceps, and brachioradialis, which were absent, while left triceps and brachioradialis were ranked $\frac{1}{4}$. Plantar reflexes showed flexion. The sensory examination was intact to light and deep touch.

Laboratory data revealed a hemoglobin of 13.5 gm/dl with an MCV of 87. The white blood cell count (WBC) was 12,800 with 80 polymorphonuclear leukocytes, 12 lymphocytes, and 8 monocytes, and the platelet count was normal. Serum sodium was 133, potassium 4.1, chloride 101, and

Tom J. Wachtel, MD, is Associate Director with the Division of General Internal Medicine, Rhode Island Hospital, Providence, Rhode Island.

bicarbonate 26 mEq/l; BUN was 27, creatinine 1.0 and, glucose 110 mg/dl. The prothrombin activity was 96 per cent. Calcium was 8.6, phosphorous 3.2, magnesium 1.9, and uric acid 5.3 mg/dl. Total protein was 7.6 and albumin was 4.1 gm/dl. Urinalysis revealed a specific gravity of 1.021, pH 7, 1/4 per cent glucose, no cells, and moderate bacteria. SGOT was 81, LDH 1372, CPK 158, and alkaline phosphatase 184 IU/L, while the bilirubin was 1.0 mg/dl. Electrocardiogram (EKG) showed normal sinus rhythm, normal intervals, left anterior hemiblock, poor R wave progression, and LVH. Chest x-ray film showed left pneumonectomy. A CT scan without contrast showed a low-density area in the right temporal parietal region of the brain.

The patient was admitted and initially treated with a high dose of dexamethasone. On the second hospital day the patient developed complete paralysis of the right upper extremity with mild weakness of the left arm and hand. He underwent a high resolution CT scan with contrast which showed a low density area in the left anterior parietal lobe. The dexamethasone dosage was further increased, and patient received 600 rads of radiation to the entire brain. He developed an episode of hyponatremia felt to be due to inappropriate antidiuretic hormone secretion (SIADH). He was treated with fluid restriction. On the 12th hospital day the patient became hypotensive, and physical examination revealed marked abdominal tenderness. A repeat (WBC) was 40,800 with shift to the left. A lateral decubitus film of the abdomen showed free intraperitoneal air. He expired on the 14th hospital day.

Discussion: Barry Miller, MD, Department of Medical Oncology, Rhode Island Hospital

This case illustrates how medical oncology is a subspecialty that covers many disciplines of internal medicine. A 65-year-old man presents with an acute neurological illness and dies three weeks later of an acute gastrointestinal complication, namely perforation. However, along the way, he is found to have cardiologic abnormalities (the EKG is abnormal) and he develops a preterminal metabolic/endocrine abnormality syndrome of inappropriate antidiuretic hormone secretion (SIADH) and a hematological abnormality (the very high white blood cell count).

A discussion of this patient's underlying diagnosis must precede any focus on the terminal events. First, he underwent a left pneumonectomy two years prior to admission for a periph-

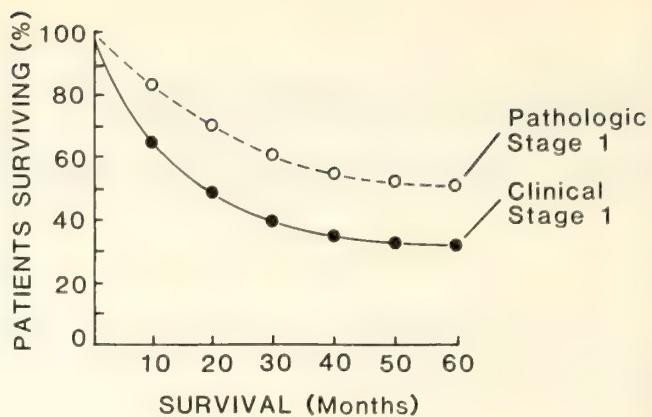


Fig 1. The survival curve for patients with clinical stage I (closed circles) and pathologic stage I (open circles) adenocarcinoma of the lung. (adapted from the American Joint Committee for Cancer Staging and End-Results Reporting²)

eral adenocarcinoma of the left lung with negative hilar nodes. The actual size of the primary tumor is not given, but, since the lesion was resectable, it is assumed that it was either stage T1 or T2. Since he had negative nodes, he had a Pathological Stage I lung cancer.¹ Second, it is important to decide whether or not the patient has recurrent adenocarcinoma of the lung. He undoubtedly suffered from recurrent carcinoma. Figure 1 demonstrates the survival results for different stages of this histological type of lung cancer as reported by the American Joint Committee for the staging of lung cancer.² It can be appreciated that this man with pathological Stage I cancer had a 50-60 per cent chance of being alive at five years and 70 per cent chance of being alive at two years. In addition, patients with resectable adenocarcinoma of the lung who die within 30 days of "curative" surgery have a 43 per cent rate of residual disease. Nearly all of this disease is manifested as distant metastases.³

Therefore, this man was very likely to relapse due to disease in distant organs, and his limited survival was almost certainly related to recurrent lung cancer. In fact, he underwent radiation therapy for a destructive lesion of the 3rd lumbar vertebra two months prior to his final illness. The x-ray film of this vertebra demonstrated a neoplastic lytic lesion. The evidence for this is the loss of a pedicle and preservation of the disk space. If there was any encroachment beyond the end-plate of the vertebra into the disk space, other causes such as infective osteomyelitis should be entertained, but loss of a pedicle is almost pathognomonic of cancer. Therefore, the patient

Table 1. Clinical Features of Bony Metastases

90% of bony metastases are multiple;
Bone scan generally more sensitive than x-rays;
30-50% of bone must be destroyed biochemically before a lytic lesion is apparent on x-ray;
Loss of vertebrae pedicle(s) with preservation of disk space nearly always indicates metastatic cancer;
Most lesions are mixed lytic/blastic in type;
Lytic lesions: myeloma, lymphoma, lung, kidney, breast, thyroid, GI, and neuroblastoma;
Blastic lesions: Prostate, Hodgkin's Disease, carcinoid, gastric, and breast.

had a lytic lesion of the vertebra which was probably secondary to the adenocarcinoma of lung. Metastases from another primary source is unlikely because there was no history of another primary lesion. Table I indicates the clinical features of osseous metastases.

Having argued that his adenocarcinoma has recurred in his bones, it is now appropriate to turn to the brain and question whether his neurological problem is related to metastases to the brain. Since he was given radiation therapy on the second or third day of his terminal admission, his physicians clearly thought that he was dealing with metastases. However, this is unlikely; and the reasons are found in the history. It is critically important to obtain a good history. Good history-taking is essential in making a diagnosis; and on examining the patient, one often knows what one is going to find.

The patient was admitted terminally with a speech problem. However, he developed neurological symptoms one week prior to admission. He had both sensory and motor symptoms with numbness and weakness in the left leg. The fact that the CT scan showed a lesion in the right parietal area excludes the possibility of a peripheral neurological problem. Since he developed a contralateral weakness and a speech problem five days later (that is 48 hours prior to admission), a central multifocal pathological process is confirmed. The time course for the onset of these symptoms is unavailable from the history. The onset was probably sudden, since the patient's wife noted something new 48 hours prior to admission, when he developed speech difficulty and weakness of the right arm. However, he may have developed this while sleeping, in which case important observations such as a seizure or loss of consciousness would not have been observed. For example, actual loss of consciousness is unusual

with cerebral thrombosis or embolism.⁴ A seizure is not an uncommon presenting episode for the first clinical manifestation of a metastasis and occurs in about 15 per cent of cases.⁵ Cerebral thrombosis commonly occurs during sleep,⁴ but we do not know whether or not the patient awoke with his new symptoms. Headache at the time of onset of his symptoms would be another important symptom to know about. For example, headache with thrombosis or embolism tends to be focal rather than global and to be present early in the morning⁵ as it is when there is a large mass effect from intracranial tumor.

In summary, this patient's problem is a multifocal central neurologic disease of relatively sudden onset. This latter feature is *not* characteristic for the presentation of cerebral metastases — which usually present as mental status change or focal deficits developing gradually over several days to weeks in the disease course.⁵ However, metastases occasionally present with stroke-like symptoms if they suddenly bleed or become necrotic.⁶ This can occur particularly with malignant melanoma or choriocarcinoma, but when this happens there is usually very marked contrast enhancement within the lesion. These diagnoses cannot be entertained here since this case showed no contrast enhancement in any of the CT scans obtained. This lack of enhancement is also an important observation in this case because most metastases show some degree of enhancement on CT scanning.⁷ Having argued strongly that this patient does not have cerebral metastases, the differential diagnosis for sudden-onset multifocal cerebral lesions must be reviewed.

Before doing this, it is appropriate to review the location of these lesions. I believe that the physical signs were not entirely consistent with what was observed on CT scan. The first lesion noted in the right parietal area produced left-leg numbness and weakness. This means that both right frontal and parietal lobes were probably involved and not just the parietal lobe. This first lesion appeared to respond well to conventional doses of dexamethasone. Was this a genuine response, or coincidental with the natural history for this disease process? This point shall be addressed later. The second lesion produced difficulty in finding words and right arm weakness — both symptoms suggesting a localized lesion in a right-handed individual, involving the cortex or subcortical area of the left inferior frontal area and precentral gyrus. This is the location of Broca's area, lesions of which produce a nonfluent expressive dysphasia which is what this patient is

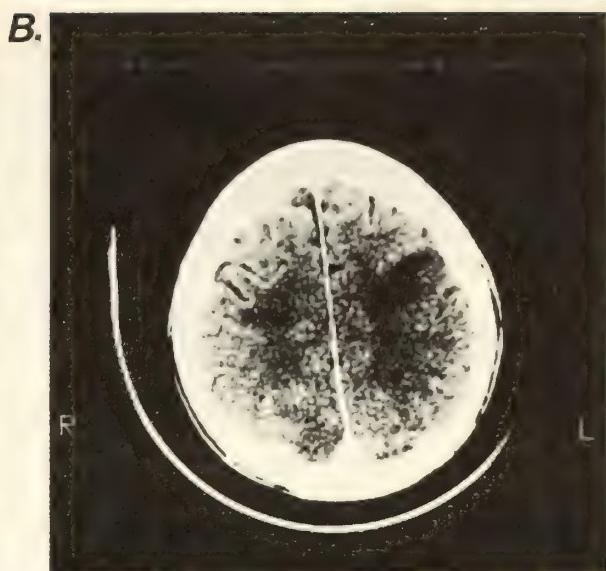
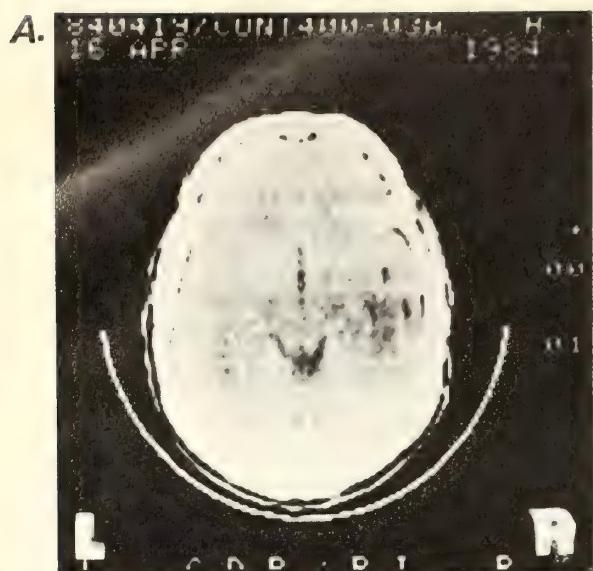


Fig 2. Representative cuts from the first cranial CAT scan demonstrating an area of low attenuation in the right parietal lobe (panel A) and from the final CAT scan demonstrating decreased attenuation in the left frontal lobe. Note that the abnormality of the right parietal lobe was not seen in this CAT scan on any of the cuts (Panel B).

described as manifesting. Also, the right arm motor area lies close by. Therefore, the signs were very focal, and the final CT scan shows a low density lesion in the left frontal area and not in the parietal lobe as described in the protocol.

The differential diagnosis for multifocal cerebral lesions is outlined in Table 2. However, since this patient's problem was of sudden onset, most conditions except the vasculitides, the demyelinating diseases, and cerebral embolism can be ruled out. Cerebral abscesses can develop fairly quickly, but we have no evidence of infection elsewhere in the body at the time of presentation. Also, the patient is afebrile, a strong point against this possibility. Furthermore, the CT scan would more than likely show enhancement, possibly with a ring-like configuration.⁸ Tuberculomas,⁹ fungal lesions,¹⁰ and syphilitic gummas¹¹ can be ruled out for similar reasons. Cerebral lymphoma will occasionally present suddenly with focal signs, but it enhances readily on the CT scan and is often seen in a periventricular location¹² or in the basal ganglia, corpus callosum, or hypothalamus.¹³ Granulomatous disease such as sarcoidosis can be ruled out, because it tends to be more insidious and usually produces cranial nerve signs.¹⁴ This leaves the three leading contenders for the diagnosis, namely vasculitis, demyelinating diseases, and cerebral embolism with multifocal emboli and infarction. Vasculitis occurs in temporal arteritis,¹⁵ but there was no evidence of temporal arterial abnormalities and no mention of headache, scalp tenderness, or low-grade fe-

ver which are often very prominent symptoms in this condition. Further, cerebral lupus¹⁵ can present with multiple small infarcts on CT scanning, but for reasons that are unclear seizures and psychotic symptoms are common with this disease. Also, lupus occurs in women nine times more commonly than in men, and therefore, is unlikely in this patient. As far as demyelinating diseases are concerned, the patient could certainly have had multiple sclerosis, but there were no other diagnostic features such as optic atro-

Table 2. Differential Diagnosis

Infective	Cerebral Abscess TB Syphilis Fungus
Lymphoma	
Vasculitides	Cranial/temporal arteritis Cerebral lupus
Granulomatous Disease	Sarcoid
Demyelinating Diseases	Multiple Sclerosis PML
Cerebral Embolism and/or Infarction	Arrhythmias Atherosclerotic plaques and TIA Mural thrombus following myocardial infarction Myxoma Infective Endocarditis Nonbacterial thrombotic endocarditis

phy or internuclear ophthalmoplegia to suggest it. In the acute stages of this disease the demyelinating lesions will often be enhanced well on the CT scan.¹⁶ Progressive multifocal leukoencephalopathy (PML) should be seriously considered because the CT scan often fails to show enhancement with these lesions.¹⁷ However, although the disease is rapidly progressive causing death within a few months, the onset is less acute than occurred in this patient.¹⁸ The clinical features and multifocality would be consistent with it, but there are no cases of PML associated with solid tumors. Nearly all reported cases of the condition have been in association with Hodgkin's Disease¹⁸ or other lymphomas,¹⁹ leukemia,¹⁹ sarcoidosis,²⁰ renal²¹ or other transplantations,²² and more recently acquired immune deficiency syndrome (AIDS) patients.²³ PML is now thought to be caused by a papovavirus.²⁴ There are also other demyelinating diseases which are very chronic or congenital and should not be given any consideration here.

Therefore, this patient could be suffering only from acute cerebral embolism with, at the least, infarction of the left frontal lobe. The time course and multifocality fit perfectly with such a diagnosis, and the CT findings are also a perfect fit. The CT changes that occur following cerebral infarction²⁵ due either to thrombosis or embolism to the cerebral vessels are shown in Table 3. There is usually little to see until 12 hours have elapsed. All the CT scans in this case were obtained probably within 48 hours of the acute symptomatic events. Hence, the only abnormality seen, particularly on the left side, was an area of ill-defined decreased attenuation in the distribution of the frontal branches of the left middle cerebral artery. Had the CT scan been repeated about one week following his admission, there would have been some enhancement, indicating so-called luxury perfusion which is seen as a cerebral infarct develops. Luxury perfusion is ac-

tually a misnomer, since it is not due to reactive hyperemia, but to breakdown of the blood-brain barrier and leakage into surrounding brain tissue.²⁶

An apparent difficulty with the CT scans is explaining the disappearance on the second and third CT scans of the right parieto-frontal lesion seen on the first CT scan. The second and third scans were performed a week after his first symptoms. The answer to this is of course easy to understand. The so-called "response" to dexamethasone is therefore very misleading. Certainly, dexamethasone can reduce the mass effect from a lesion and produce symptomatic benefit, but it rarely makes a lesion almost completely disappear. The first lesion represented another embolus, which produced transient symptoms and a transient low-density area on the first CT scan, which then disappeared simply because the embolus broke up following its lodgement and caused no permanent effects — the classical transient ischemic attack affecting the right hemisphere. Unfortunately, a week later the embolus to the left hemisphere did not break up and indeed appears to have progressed to infarction, which on the second hospital day became clearly manifested with total right upper monoplegia. Dexamethasone this time had no effect, and the first apparent response to this medication was obviously non-existent. Incidentally, the third CT scan may also show additional embolization to the right occipital area.

Hence, if this man was suffering from repeated embolization to the brain, is there evidence for embolization to other organs? And where were these emboli originating?

First, what is the evidence for other organ involvement? The protocol gives us no valuable symptoms or signs for this, such as splinter hemorrhages, splenic enlargement, or flank pain, but the laboratory data possibly indicate some other organ involvement in the patient's embolic process. Red cells were noted in the urine, indicating possibly a small renal infarct, and the cardiac enzymes were elevated — the CPK is moderately elevated. Although, it could be coming from the brain rather than from the heart. However, at the time of this elevation, a full-blown cerebral infarction had not yet developed. The SGOT and LDH are elevated to 3-4 times normal value, suggesting that any embolus producing coronary artery ischemia and myocardial infarction may be several days old. The patient did not complain of chest pain, but the EKG indicates a left anterior hemiblock, among other changes, which

Table 3. CAT Scanning for Vascular Stroke²⁵

0-12 hrs	— Usually little to see;
12-48 hrs	— Decreased attenuation in distribution of vessels. Ill defined border;
2-5 days	— Borders better defined due to edema Wedge shape may appear extending to cortex Usually little contrast enhancement;
4 days-4 weeks	— Enhancement appears and usually is subsiding by 4 weeks. Enhancement occurs mainly in grey matter and is due to breakdown of blood-brain barrier.

could conceivably have been caused by a small myocardial infarction. This is mentioned only as a possibility, because the elevated SGOT and LDH could have been due to or contributed to by liver metastases especially since the alkaline phosphatase was also elevated. Whichever is the case, no isoenzyme patterns are given for any of these enzymes. Therefore, it is impossible to sort this out with any certainty. In summary, embolization to the kidneys and left coronary vessels is a possibility in addition to that in the brain.

Secondly, what was the source of embolization? It must be the heart to have produced this clinical picture. Table 2 summarizes the sources of cerebral embolization. Arrhythmia can be ruled out, since it is not described in the protocol. Atherosomatous plaque is excluded, since plaque usually embolizes repeatedly to the same area of the brain or retina. The possibility of mural thrombus from myocardial infarction is a viable one, but most such thrombi occur in large myocardial infarcts, which would have been manifested by chest pain and characteristic electrocardiographic changes. Myxoma is extremely unlikely, and infective endocarditis is ruled out by the lack of any fever. This leaves nonbacterial thrombotic endocarditis, which this patient probably suffered from and which caused all of his problems and his ultimate demise. The disorder is also known as marantic or verrucous endocarditis.²⁷

Nonbacterial thrombotic endocarditis is an entity about which there are exactly three lines of text in Harrison's Textbook.¹⁵ It occurs in autopsy series in 4-5 per cent of patients with disseminated cancer²⁸ and is four times more likely to occur in cancer patients than in those with other diseases.²⁸ It occurs particularly in patients who have disseminated adenocarcinoma.^{29, 30} The adenocarcinoma is frequently mucin-producing.³¹ Premortem cardiac murmurs, usually soft systolic murmurs best heard at the left sternal border, are noted in only a third of autopsy documented cases.³⁰ Adenocarcinoma of the lung is the most frequent underlying carcinoma (7-8 per cent of cases³⁰), but other cancers, particularly of the gastrointestinal tract, prostate, and breast can be the cause.³⁰ The lesions consist of platelet-fibrin vegetations on the mitral and aortic valves³² — the mitral probably being the most common.³⁰ There are some reports suggesting that the valves must be damaged a priori for these vegetations to occur,²⁹ but this is a controversial point.

Patients experience embolization to many organs, but particularly to the brain³³ and to a lesser degree, to the spleen, the kidneys, and the cor-

onary arteries.^{30, 34} The gut can occasionally be embolized³⁰ which may have some relevance for this patient.

The presence of platelets and fibrin in the vegetations suggest that these patients may suffer from a hypercoagulable state,^{29, 35} which is not easily detected clinically. This hypercoagulable state causes a clinical spectrum which includes no manifestation, fibrinous vegetations on the heart valves as above, chronic disseminated intravascular coagulation (DIC), acute DIC, and even venous thromboembolism²⁹ (the syndrome described by Trouseau). All of these coagulopathies are seen regularly in patients with disseminated adenocarcinomas. They may be related to production of thromboplastic substances by malignant glandular tissues, but the exact pathophysiology is still unknown.

Therefore, this 65-year-old man had recurrent disseminated cancer in his bones and probably in his liver. He had a hypercoagulable state leading to nonbacterial thrombotic endocarditis embolizing to the brain, kidneys, and possibly the coronary vessels.

Finally, the terminal events must be discussed. The patient clearly developed peritonitis and this was due to perforation of the bowel. The perforation was most likely at the site of a stress-induced peptic ulcer related to his profound neurological problems. This kind of problem is not uncommon with severe cerebral injury of any kind.³⁶ Incidentally, SIADH is also common with severe cerebral injury — as demonstrated in this patient. Steroids should not be implicated as the cause of perforation since Conn had demonstrated several years ago³⁷ that steroids have no relationship with the development of peptic ulcer. There is also a remote possibility that perforation was due to a bowel embolization. Whichever was the case, the resultant peritonitis produced a leukemic reaction which was the terminal laboratory abnormality associated with the patient's terminal illness.

Dr. Barry R. Miller's Diagnosis:

1. Peritonitis
2. Perforation of stress-induced peptic ulcer
3. Adenocarcinoma (mucinous?) of the lung with bony and hepatic metastases
4. Hypercoagulable stress
5. Nonbacterial thrombotic (verrucous or marantic) endocarditis of mitral and probably aortic valves with embolization to the brain, kidneys, and possibly the coronary arteries.

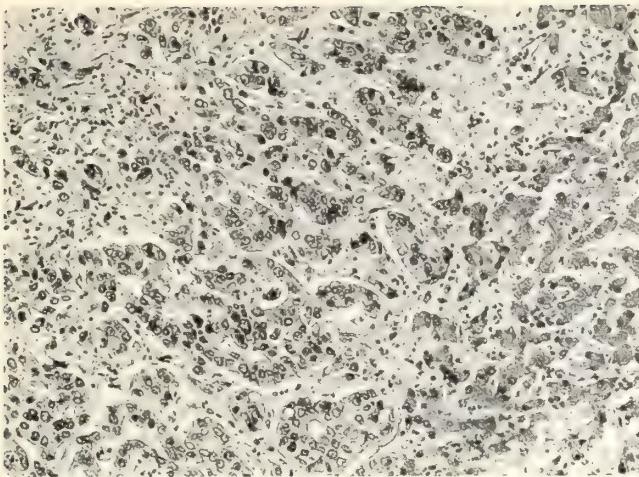


Fig 3. A section of the liver demonstrates a metastatic adenocarcinoma, moderately differentiated in this photomicrograph. Mildly and slightly inflamed hepatic parenchyma is present at the right side of the field. Infiltrating tumor covers most of the section with some gland formation discernable.

Pathology Discussion: Harvey F. Sasken, M.D., Department of Pathology

Review of the surgical slides from the previous left pneumonectomy confirmed the diagnosis of pulmonary mucin-producing adenocarcinoma. At necropsy examination metastases were noted in the right lung, liver, lymph nodes, and bone (including vertebra). The tumor is moderately to poorly differentiated, with occasionally demonstrable gland formation (Figure 3).

Severe arteriosclerotic cardiovascular disease was present. There was an acute myocardial infarction in the posterolateral left ventricle, with regions compatible with evolution from three days to over one week. Further examination of the heart revealed a nonbacterial thrombotic endocarditis (marantic endocarditis). Vegetative lesions were confined to the aortic valve, but were present on the free surfaces of all three leaflets. The lesions were shaggy, granular, focally conglomerate, and focally friable. Microscopic examination of the valve revealed lesions containing swollen collagenous tissue with fibrinoid deposition associated with small vasculature. Rare inflammatory cells were present. Bacteria were not identified (Figure 4). In some areas shaggy vegetations composed of protein and platelet accumulation were present adherent to the valve surface. These were also free of bacteria and contained few inflammatory cells.

Thromboemboli were present in the brain together with cerebral and cerebellar infarcts.



Fig 4. Microscopic examination of the aortic valve leaflets reveal swollen collagenous fibers and fibrinoid alteration. Minimal inflammation is present. This section suggests accumulation of fibrinous material from a vascular source within the tissue. Other sections reveal bland thrombotic material on the valve surface.

There were no central nervous system (CNS) metastases. Thromboemboli were also present in the lung, without evidence of infarction. Early organization and adhesion to the vascular wall is present in these lesions (Figure 5).

Other significant findings at necropsy include a pyloric ulcer with perforation and an associated serositis. Chronic obstructive pulmonary disease was also documented.

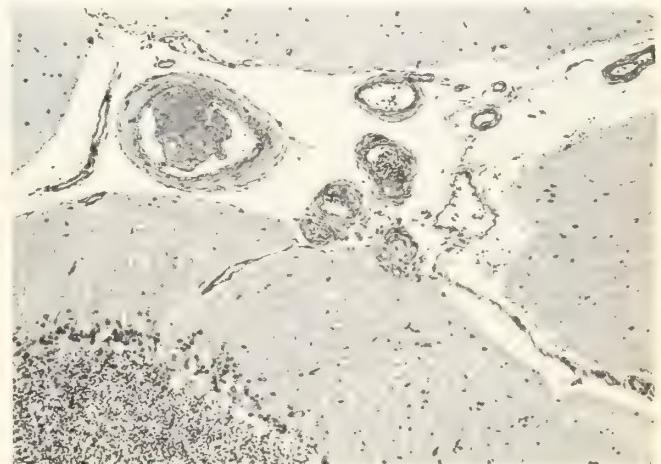


Fig 5. Multiple acute cerebral and cerebellar infarcts were present. This photomicrograph of the cerebellum demonstrates a central polypoid thromboembolysis with surface endothelialization and subjacent cortical rarefaction as evidence of an acute infarction.

Anatomic Diagnosis

1. Pulmonary adenocarcinoma, left lung, with metastases to the right lung, liver, vertebral column, and lymph nodes.
2. Arteriosclerotic cardiovascular disease, with acute myocardial infarction.
3. Nonbacterial thrombotic endocarditis (marantic).
4. Cerebral and cerebellar infarcts, multifocal.
5. Pulmonary thromboemboli.
6. Pyloric ulcer, with perforation and serositis.

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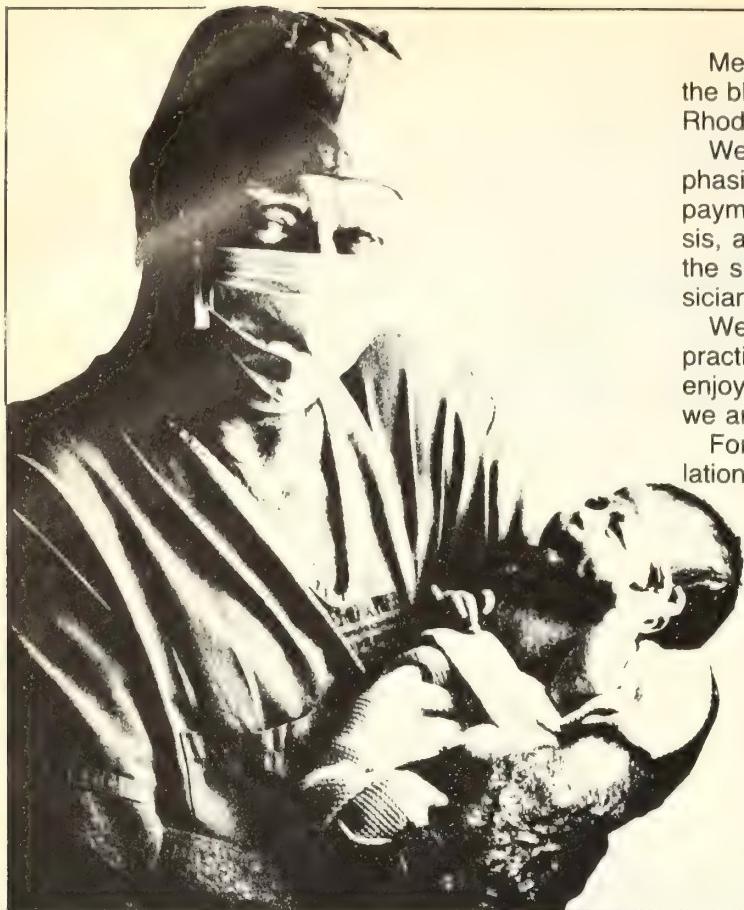
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—FORTHCOMING PUBLICATION—

Yankee Surgeon: The Life and Times of Usher Parsons, 1788-1868, by Seebert J. Goldowsky, M.D.

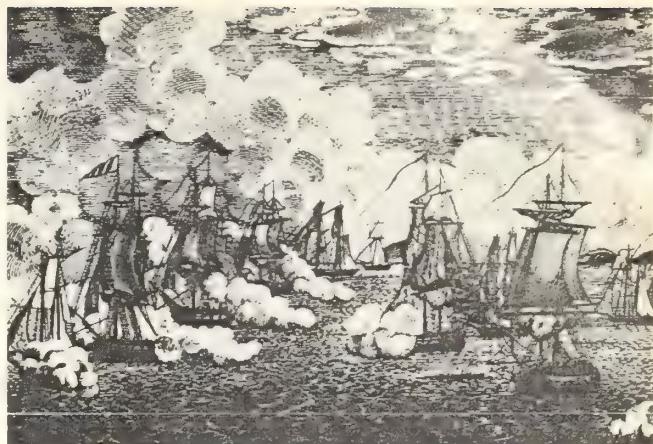


Usher Parsons, MD (1788-1868)

This September, the Boston Medical Library will publish a biography of the Rhode Island surgeon and ship's physician Usher Parsons. Born in Maine and educated in medicine in the apprenticeship system prevalent in his day, Dr Parsons concluded his training just in time to land a berth on a War of 1812 frigate destined for Lake Erie to hold the northern frontier from the Canadians and British. Befriended by Oliver Hazard Perry and serving in Perry's squadron, he not only participated in the historic Battle of Lake Erie as the only surgeon in Perry's fleet but later wrote a detailed account of the battle — the one which historians have come to accept as the most authentic and reliable. In all, Parsons spent ten years as a naval surgeon, making several cruises to the Mediterranean with Perry, Captain Thomas Macdonough and other early naval figures to uphold the rights of the United States in that region, especially against Algerian infringements. His surgeon's logs, diaries and letters comprise a rich store of information on early American naval lore, sea life in those times, and naval medicine.

Between his several tours abroad, Parsons

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The Battle of Lake Erie, 1813

managed to wangle duty at the Charlestown Naval Yard in order to matriculate at the Medical Department of Harvard University, from which he graduated in 1818. After his separation from the service, he settled in Providence, Rhode Island, teaching at the Medical School of Brown University until its dissolution in 1827 and practicing surgery throughout the remainder of his life. In 1821 Dr Parsons married Mary Jackson Holmes, the elder sister of Oliver Wendell Holmes; Mary's many letters home to her family in the years before her premature death give us an intimate glimpse of what a woman's life was like in those days. Despite his busy practice and participation in the affairs of the Rhode Island Medical Society and the incipient AMA, Parsons found time to explore antiquarian interests and to write, most notably a biography of Sir William Pepperrell who captured Louisbourg, the French stronghold on Cape Breton, during the expedition against Canada in 1746. The major achievement of the last part of his life was the establishment of the Rhode Island Hospital in 1868, just prior to his death.

Seebert J. Goldowsky, the author of *Yankee Surgeon*, is a graduate of the Harvard Medical School, a former practicing surgeon in Providence, and current editor of the *Rhode Island Medical Journal*. His biography of Dr Parsons is being published by the Boston Medical Library in association with The Rhode Island Publications Society.

Comprising more than four hundred printed pages and containing three dozen illustrations, *Yankee Surgeon* will be priced at \$24.50 but will be offered at a prepublication price of \$22.00 prepaid. To reserve or order your copy, send a check to Science History Publications/USA, our distributor, at Post Office Box 493, Canton, Massachusetts 02021 (telephone: 617-828-8450).

BOOK REVIEW

Allergy

Food Allergy: A Primer for People, second edition, S. A. Bock, Vantage Press, Inc., New York, 66 pp., hardcover, \$8.95, 1988.

The second edition of this book, like its predecessor, is intended to provide sound information of food allergies to the educated layperson. The second edition updates the first in regard to new research in the field and discusses some of the newer food allergy fads that patients may read or hear about. Examples are sublingual food drops, cytotoxic food testing, food injections, skin testing and dietary treatments such as the Feingold diet and the "Yeast-hypersensitivity Syndrome" diet.

An expert in the field, Dr Allan Bock is to be congratulated on presenting scientific, well-documented facts regarding food allergies and simplifying the complexities into lay language. Dr Bock's style of writing is engaging and illustrates points made with case examples. The book exposes and critiques fads and fallacies regarding food allergies, and defines allergy and the allergic response. It also includes information on adverse reactions to food and describes the basic principles of antigen/antibody reaction. A discussion of reliable and unproven diagnostic testing methods and treatments as mentioned in the examples above is especially helpful. Dr Bock makes the points that food allergies are uncommon and can only be confirmed through double-blind food tests and that testing methods vary in their specificity, sensitivity and reliability. Dr Bock also encourages readers to ask their personal physicians questions to facilitate good communication between doctor and patient in problem solving. A glossary and reference list are provided for readers who need help with medical terminology and who wish to explore the subject in greater depth.

The book's content is excellent. In a field that abounds with myths and misinformation, the author clearly and succinctly sets the record straight. The addition of illustrative material such as drawings, tables and graphs in appropriate spots placed strategically throughout the text would have added to its marketability.

This book should be included as recommended reading material for patients who have questions about food allergies. It would serve as a fine addition to a patient education lending library in physician's offices. The reading level is fairly high. A patient with less than a 12th grade education with a basic biology background may have problems comprehending the content. Overall, the book is sound, factual and concise and is welcome in a body of lay literature that is confusing at best.

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Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (penicillinase and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, and *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexenae*,* and *Shigella sonnei** when antibacterial therapy is indicated.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with Cipro® may be initiated before results of these tests are known, once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN OR PREGNANT WOMEN. The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and very rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals. Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded. Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

Drug Interactions

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosages adjusted as appropriate.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired. Concurrent administration of these agents with ciprofloxacin should be avoided.

Probencid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients

Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum concomitantly or within two hours after dosing. Ciprofloxacin may cause dizziness or lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:

Salmonella/Microsome Test (Negative)

E. coli DNA Repair Assay (Negative)

Mouse Lymphoma Cell Forward Mutation Assay (Positive)

Chinese Hamster V₇₉ Cell HGprt Test (Negative)

Syrian Hamster Embryo Cell Transformation Assay (Negative)

Saccharomyces cerevisiae Point Mutation Assay (Negative)

Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)

Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the following three *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay

Micronucleus Test (Mice)

Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in animals have not yet been completed.

Pregnancy - Pregnancy Category C

Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in

CONVENIENT B.I.D. DOSAGE

Recommended dosage schedule

Infection Site*	Severity of Infection	Dosage
Respiratory Tract*	Mild/Moderate	500 mg B.I.D.
Bone and Joint*		
Skin/Skin Structure*	Severe/Complicated	750 mg B.I.D.
Urinary Tract*	Mild/Moderate	250 mg B.I.D.
	Severe/Complicated	500 mg B.I.D.
Infectious Diarrhea*	Mild/Moderate/Severe	500 mg B.I.D.

pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers

It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this, and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Ciprofloxacin should not be used in children because it causes arthropathy in immature animals (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%).

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below. Those typical of quinolones are italicized.

GASTROINTESTINAL (See above), painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM (See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, mania, reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.

SKIN/HYPERSensitivity (See above), pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

SPECIAL SENSES blurred vision, disturbed vision, change in color perception, overbrightness of lights, decreased visual acuity, diplopia, eye pain, tinnitus, bad taste.

MUSCULOSKELETAL joint or back pain, joint stiffness, achiness, neck or chest pain, flare-up of gout.

RENAL/URINARY interstitial nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY epistaxis, laryngeal or pulmonary edema, hiccup, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Adverse Laboratory Changes Changes in laboratory parameters listed as adverse events without regard to drug relationship.

Hepatic - Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Hematologic - eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal - Elevations of Serum creatinine (1%), BUN (0.9%).

CRYSTALLURIA, CYLINDURIA, AND HEMATURIA HAVE BEEN REPORTED

Other changes occurring in less than 0.1% of courses were: elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. In the event of serious toxic reactions from overdosage, hemodialysis or peritoneal dialysis may aid in the removal of ciprofloxacin from the body, particularly if renal function is compromised.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro® (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and in Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE INFORMATION).

* Due to susceptible strains of indicated pathogens. See indicated organisms in Brief Summary.

For further information, contact the Miles Information Service: 1-800-642-4776. In VA, call collect: 703-391-7888.

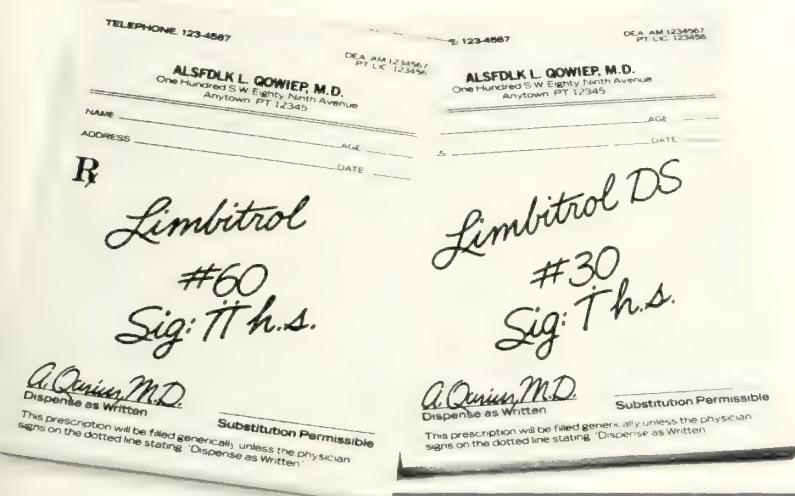
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Limbitrol® DS
Each tablet contains 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) **(IV)**

References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Feighner VP, et al: Psychopharmacology 61:217-225, Mar 22, 1979.

Limbitrol®

Tranquiler—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants; concomitant use with MAOIs or within 14 days of monoamine oxidase inhibitors (then initiate cautiously, gradually increasing dosage until optimal response is achieved); during acute recovery phase following myocardial infarction.

Warnings: Use with caution in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur when used with anticholinergics. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia, prolongation of conduction time, myocardial infarction and stroke reported with tricyclic antidepressants, especially in high doses. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs: **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. **Neurologic:** Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extra-pyramidal symptoms, syncope, changes in EEG patterns. **Anticholinergic:** Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. **Allergic:** Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus. **Hematologic:** Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. **Endocrine:** Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (anti-diuretic hormone) secretion. **Other:** Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Overdosage: Immediately hospitalize patient. Treat symptomatically and supportively. I.V. administration of 1 to 3 mg physostigmine salicylate may reverse symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

How Supplied: Double strength (DS) Tablets, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and Tablets, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.



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See Improvement In The First Week¹... And The Weeks That Follow

- 74% of patients experienced improved sleep after the first *h.s.* dose¹
- First-week reduction in somatic symptoms¹

Caution patients about the combined effects of Limbitrol with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car. In general, limit dosage to the lowest effective amount in elderly patients.

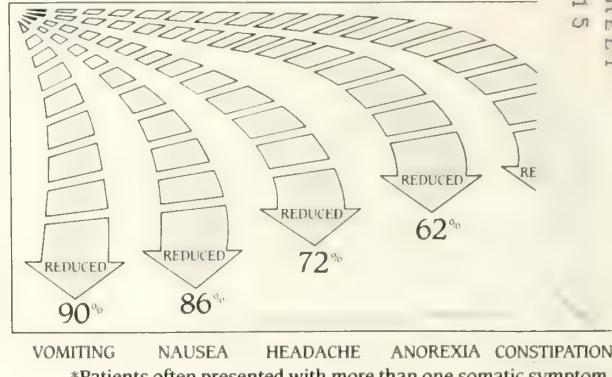
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Limbital DS®

Each tablet contains 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) (IV)

Percentage of Reduction in Individual Somatic Symptom During First Week of Limbitrol Therapy*



*Patients often presented with more than one somatic symptom.

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Please see summary of product information inside back cover.



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LEVI C. ADAMS

Associate Vice President for External Affairs
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Brown University
Providence, RI
(See page 351)

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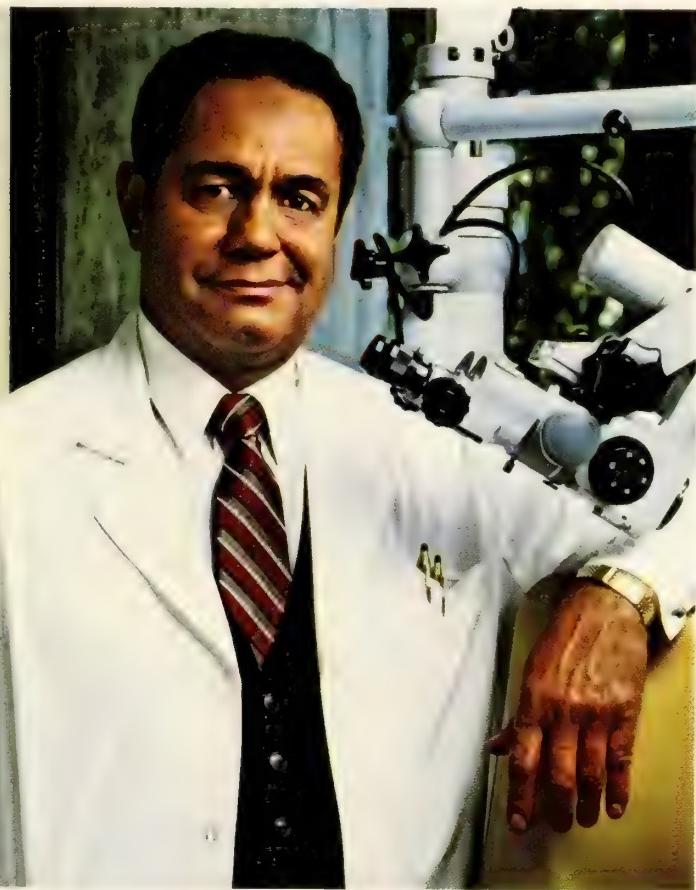
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DALE L. TIPTON, M.D.

Associate Clinical Professor, Department of Otolaryngology, Head and Neck Surgery, University of California School of Medicine, San Francisco, California.

Chairman, Division of Otolaryngology, Franklin Hospital, San Francisco, California.

Lieutenant Colonel, U.S. Army Reserve.

EDUCATION University of California at Berkeley, A.B. Physiology; University of California School of Medicine, San Francisco, M.D. and Master of Science, Pharmacology.

RESIDENCY University of California School of Medicine, San Francisco: General Surgery – 2 years; Otolaryngology – 3 years.

FELLOWSHIPS National Institute of Health Fellow; Cancer Research Institute, University of California, San Francisco.

OUTSTANDING ACHIEVEMENTS Freshman Medical Student Research Award; Class President – 2nd year medical school; Student Body President – senior year medical school; Special Award by National Institute of Health to attend and present paper at International Congress of Otolaryngology in Tokyo, Japan; Chairman, Department of Otolaryngology, San Francisco General Hospital 1970-76; Chief of Medical Staff, Franklin Hospital 1982-84.



Dr. Tipton and residents examining post-operative patient in recovery room.

"I joined the Army Reserve shortly after completing my responsibilities as Chief of Staff of Franklin Hospital in San Francisco. I was intrigued with the idea of trying something different, such as Army Medicine.

"I find that the challenges and rewards of serving as an Army Reserve physician complement my civilian practice. For a number of years, I've been teaching as a member of the Clinical Faculty at the University of California School of Medicine, and I thoroughly enjoy the many teaching opportunities available to me in the Reserve. It is a rewarding experience to be involved in the training of Army medical students, interns, and residents. I also enjoy interacting and exchanging information with full-time Army physicians and seeing a wide variety of interesting clinical cases."

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for better patient compliance



AXID®

nizatidine capsules

Brief Summary. Consult the package insert for prescribing information.

Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

Axid is indicated for maintenance therapy for duodenal ulcer patients, at a reduced dosage of 150 mg h.s. after healing of an active duodenal ulcer. The consequences of continuous therapy with Axid for longer than one year are not known.

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H₂-receptor antagonists.

Precautions: General—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions—No interactions have been observed between Axid and theophylline, chlorazepoxide, lorazepam, lidocaine, phenytoin, and warfarin.

Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxytic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high dose males compared to placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement

compared to concurrent controls, and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive, and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery is not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, and the mouse lymphoma assay.

In a two-generation, perinatal and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—**Pregnancy Category C**—Oral reproduction studies in rats at doses up to 300 times the human dose, and in Dutch Belted rabbits at doses up to 55 times the human dose, revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weight. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydronephrosis, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Nizatidine is secreted and concentrated in the milk of lactating rats. Pups reared by treated lactating rats had depressed growth rates. Although no studies have been conducted in lactating women, nizatidine is assumed to be secreted in human milk, and caution should be exercised when nizatidine is administered to nursing mothers.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions—Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among the more common adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs <0.1%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported. It was not possible to

determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antidiuretic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic—Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H₂-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs.

Integumentary—Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients. Rash and exfoliative dermatitis were also reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported.

Overdosage: There is little clinical experience with overdosage of Axid in humans. If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

Test animals that received large doses of nizatidine have exhibited cholinergic type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous LD₅₀ values in the rat and mouse were 301 mg/kg and 232 mg/kg respectively.

Axid® (nizatidine, Lilly)

Eli Lilly and Company
Indianapolis, Indiana
46285

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Axid® (nizatidine, Lilly)

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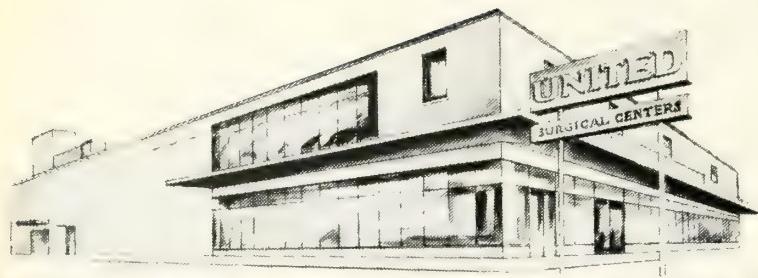
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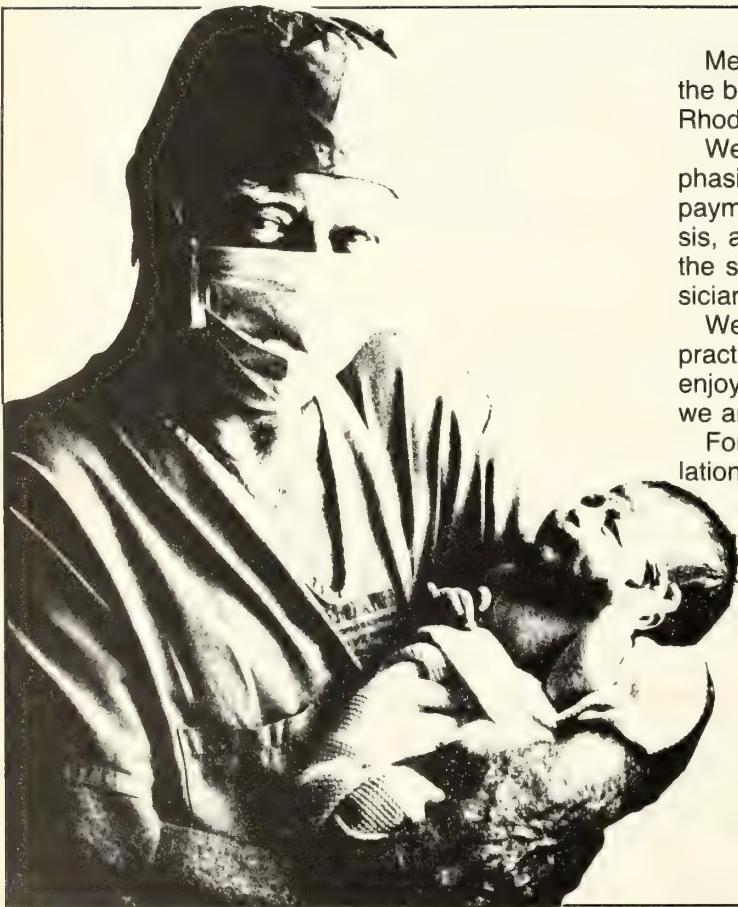
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Cover: Photo of Levi C. Adams, Associate Vice President for External Affairs with the Division of Biology and Medicine at Brown University, addressing the Brown University Program in Medicine Class of 1988. Courtesy of Brown University, Providence, RI. See page 351.

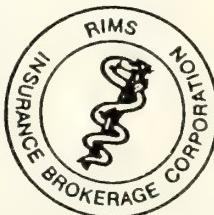
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EDITORIALS

The Rhode Island Cancer Registry

In the present issue of the *Rhode Island Medical Journal* is a paper by Fulton, Buechner, Stanis, and Raimondo on a cancer registry for the State of Rhode Island. The article is not a presentation of data to characterize cancer in Rhode Island at this time; rather, it is an invaluable discussion of the requirement for quality assurance of data in the registry based on the experience in Rhode Island for the first six months of data collection. It is written by experts in the fields of biomedical data collection, assurance of quality, and computerization. The article is an important contribution to cancer control in Rhode Island as well as elsewhere.

In the years 1977-1982, the National Cancer Institute (Bethesda, MD) supported a demonstration project on cancer control in Rhode Island. A central part of the project was the establishment and operation of a population-based cancer registry for the state. While through the hard work of experts in the field some data from that registry were retrieved and compiled in usable form, the project was less than successful because the strict requirements for the establishment and operation of a registry were not in place before the beginning of the project as emphasized by Fulton et al in this issue of the *Journal*.

Clearly, the operation of a registry which could serve as an informational source for those interested in cancer and which could serve as a "public health tool" for epidemiologic studies entails a considerable effort and expense. Some six years ago, the Rhode Island Department of Health, the Hospital Association of Rhode Island, the Rhode Island Foundation, and Blue Cross/Blue Shield

began to explore ways and means for such financial support. However, the Rhode Island General Assembly in its January 1985 session, recognizing the great importance of cancer especially in Rhode Island, amended Chapter 23-12 of the General Laws entitled "Cancer" to establish a "Central Cancer Registry." The law took effect on 1 July 1985. It detailed provisions for the financial support of the Registry and very carefully defined the protection of confidentiality. Cancer again became a reportable disease in Rhode Island and in the domain of public health.

The act included the significant statement, "The state director of health shall conduct such activities to prevent and to control cancer among the residents of the state as he shall deem necessary and appropriate and as are indicated from the findings of the central cancer registry." For this purpose, quarterly audits of the collected data are made. The cancer registry cannot be a static one-year undertaking, but must be operated on a dynamic continuing basis. The annual data obtained may demonstrate trends, but comparisons of five-year and ten-year blocks of data are needed to show the impact of efforts at early diagnosis of cancer in the community and the effects of new and improved forms of treatment.

The Rhode Island Department of Health can be justly proud of its cancer registry with a firm basis of financial support and with a very strong operational organization for quality control of the computerized data. The registry merits credibility and can justify the respect of the entire medical community. The personnel involved are ideally suited to the undertaking.

The registry described here by Fulton et al may

impress the reader as an entirely new concept for state cancer control. The need for a registry in cancer control certainly is not a new concept. It is noteworthy that our neighbor State of Connecticut has operated an excellent registry for some 50 years and some of us operated a single-hospital punch-card type of registry in another city as early as 1951. The techniques were primitive as compared with the present Rhode Island registry, but the conceptual necessity for a registry was important then as it is now. The need for a cancer registry in order to do epidemiological work in the State of Rhode Island was aptly emphasized, sometimes vociferously, by the National Cancer Institute's Rhode Island Cancer Control Program of 1977-1982. Indeed, some of us believe that the activities of that program in relation to the necessity for a registry may have become known to our legislators who did pass the amendment to 85-S0742 entitled, "An Act Relating to Cancer" in the General Assembly, January 1985 Session. The efforts of the Rhode Island Cancer Control Program (1977-1982) did leave a legacy.

Commitment to a cancer registry which will be useful for epidemiological studies in the state is necessarily long-term. Many believe that cancer may be, for the most part, a preventable disease. However, to discover the causative items is a long-time proposition. Effects do not become apparent overnight or after days, weeks, or months. Demonstrations of causes and effects require years or decades. A cancer registry, therefore, must be a long-term continuing operation. Surely, conducted as described in the article in this issue of the *Journal*, the results will be credible, of high scientific value, and well worth the effort.

Fiorindo A. Simeone, MD

Increasing Organ Donor Awareness

Since the first successful kidney transplant was performed in 1954, there have been continual gains in the field of organ transplantation. New technology and further developments of immunosuppressive drugs add to the success of these operations. Yet, the number of patients awaiting organ transplants far exceed the availability of possible donors.

Revisions in the Uniform Anatomical Gift Act (1968), "required request," were recently created

to increase the number of available donors. The required request laws now in effect direct hospitals to develop specific guidelines for organ donation and designate individuals to assist families in the process. Enactment of this legislation also allows families to make the choice between voluntary donation and refusal.

Health-care professionals involved in organ donation and transplantation must be familiar with their hospital's policy concerning this process. Organ-donor protocols should provide adequate legal guidelines and protection for hospital staff. It is also necessary to understand the organ recovery criteria (ie heart, liver, kidney) as well as the means for determining brain death.

Often, the critical care nurse assumes the role of "requester"—the person designated to speak with a family concerning organ donation. An important factor here is timing. Families must be apprised of the news of poor prognosis before being approached about donation. A helpful opener to the conversation could be a question such as "Did he/she ever express a wish to donate organs?" It is also important to understand a family's religious beliefs. Many individuals harbor various fears in connection with organ transplants. Effective communication between the "requester" and the donor family can help to create a better understanding of the process. Organ donation is often viewed by many as a gift of life. Making this choice can be a way of having something positive come from the loss.

This month's issue of the *Journal* contains an AMA report on the status of the organ procurement system nationally and intention of the AMA to review the federal study on required request laws. Efforts to promote public awareness are taking on a more organized approach with several groups, such as the National Kidney Foundation, using the media to educate communities. Similar efforts were evident during this year's Organ Donor Awareness Week celebrations which were held April 24-30.

In May of this year, a bill (S. 2409) was introduced by Senator Dale Bumpers (D-AR) as the "Cooperative Organ Transplant Contributions Act of 1988." This bill would establish a National Organ Transplant Trust Fund. The bill would allow for a fund to be financed by voluntary check-off on federal income tax returns. Each state would receive funds donated by its citizens, which would supplement the costs of transplants and immunosuppressive drugs. This bill is being supported by the American Council on Transplantation and other related organizations.

A clearly stated hospital policy concerning organ donation and transplant along with a sensitive approach on the part of the health-care professional responsible for dealing with donor families will help to increase organ availability. Locally, RIMS president Dr Boyd King has met with Senator Paul Sherlock and Mary Ellen McNally, the Organ Donation Coordinator for the New England Organ Bank, to explore ways in which the Medical Society can help in this vital area. A Donor Awareness Committee is also being formed, to be headed by Senator Sherlock. Through such efforts the organ donor and transplant program should see positive results.

Kimberly J. Allyn



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1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
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Assuring the Quality of Cancer Registration in Rhode Island

Evaluation of Early Returns Indicates Future Measures for Enhancing Reliability

John P. Fulton, PhD
Jay S. Buechner, PhD
Dorothy Stanis, AS
Marianne Raimondo, MS

The Rhode Island Cancer Registry (RICR) is founded on a comprehensive quality assurance program to protect the integrity of its data and to maximize its usefulness as a public health tool. The registry began collecting reports on newly diagnosed cases of cancer in October, 1986 with the quality assurance program in place. Six months' registry data have been collected, checked, and audited, allowing a thorough evaluation of the effectiveness of quality assurance measures.

Cancer registration, a fundamental public health tool, entails the systematic collection of information on specified neoplasms for a de-

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fined population. Such information may be used for surveillance, epidemiology, evaluation, and planning. If the population from which a registry draws information is defined geographically, registry data may be used to compute cancer incidence rates and other morbidity rates for a geographic region.¹ The RICR draws information from the resident population of Rhode Island, although information is also collected on non-residents who are diagnosed as having cancer or are treated for cancer in the state.

Cancer registration is a complex process, even if limited to the patient population of a single health care facility. In a hospital information must often be gleaned from fragmented record-keeping systems, to which many clinical, laboratory, and clerical personnel contribute. The completeness of clinicians' notes varies widely, and record linkages may be omitted. Inquiries may be needed to flesh out ambiguous or incomplete records.

Cancer registration is more complex if extended beyond individual facilities. The RICR collects data from more than 30 health care facilities. It encounters many differences among medical records systems and works to standardize the timing, completeness, and accuracy of case reports. The registry strives to register each case only once. It investigates new sources of case reports and combines reports of individual cases.

The complexities of cancer registration spawn error. Case reports may be incomplete, inaccurate, omitted, or redundant. Errors must be avoided, or, if found, corrected. Otherwise, statistical aggregates may be compromised, resulting in morbidity rates that are too high or too

low for a given geographical area, population subgroup, or type of cancer.

To protect the integrity of cancer statistics, cancer registries incorporate quality assurance procedures. While these vary among registries, they usually have similar goals. These include monitoring the completeness of case reports, triggering queries when necessary, checking the accuracy of the information, finding omitted cases, and combining duplicative case reports.²

Using six months' registry data, the effectiveness of the Registry's quality assurance program has been analyzed in detail, including a comparison of cancer incidence estimates as between Rhode Island and Connecticut. On the whole, data processed thus far by the registry have been timely. After checking, correcting, and auditing, case reports are substantially complete and accurate. Nearly all newly diagnosed cases of cancer appear to have been registered. Overall, the quality assurance program has worked well, but will be modified on the basis of quality assurance findings thus far.

The Rhode Island Cancer Registry Quality Assurance Program

Background. The RICR, the official statewide cancer registry of Rhode Island, was established by the state legislature in 1985. The registry officially began operations on October 1, 1986. All malignant and *in situ* neoplasms (with few exceptions) diagnosed in Rhode Island on or after that date are reportable. The registry has reciprocal data-sharing agreements with the state cancer registries of Connecticut, Massachusetts, and New Hampshire to identify Rhode Island residents who are diagnosed in these three states as having cancer.

The Rhode Island Department of Health (RIDH) contracts with the Hospital Association of Rhode Island (HARI) to collect, check, and computerize cancer case reports. HARI also provides training and technical assistance to all facilities reporting to the registry, including on-site auditing of ten per cent of case reports, a focus of on-going registrar education. HARI transfers computerized case reports to the Department, where they are re-checked, analyzed and publicized.

Principles. The quality assurance program of the RICR is founded on four basic principles of evaluation:

- *The most important step to assure the quality of a program is to plan properly in the first place.* The rules and regulations of the Registry (reviewed

and approved by participating health facilities), as well as procedures followed by HARI and RIDH staff, have been designed to avoid confusion and error.

- *Quality assurance programs should focus primarily on program outcomes and secondarily on program structure and processes.* The quality assurance program measures the completeness of case reports, the accuracy of reported information, and the omission or redundancy of case reports.

- *The evaluation of a program must be designed to guide and modify the program.* Quality assurance measures are computed quarterly and are used to make administrative decisions about data collection and registrar support and training.

- *Evaluation results must be delivered directly and effectively to those persons who will actually modify the program.* This is accomplished in two ways. Regular audits are conducted in the presence of institutional registrars to check their work and to build registration skills. Workshops on special problems are held for institutional registrars.

Completeness of Information. The Rules and Regulations of the RICR specify 19 items of information which must be completed in a case report. Incomplete case reports may be submitted if necessary, but the registry works in a number of ways to achieve completeness.

The procedure manual of the RICR describes various sources of information for case reports. It has been distributed to all institutional registrars. Reference to the manual is made when questions are answered by HARI staff. It is also used in workshops for institutional registrars.

Each case report is checked for completeness of information. If the report indicates by means of a special code that an item of information is unavailable, the case is accepted, but the missing information is noted. If the report indicates, by means of a blank that an item is missing, the registrar is queried to determine if the information is truly unavailable. About one third of all queries yield additional information.

RICR may receive more than one report per case, because of diagnosis or treatment at more than one institution. Redundant case reports are merged to form composite case reports. The latter tend to have less missing information than individual reports, because information unavailable to one institution may be available to another.

Audits are performed on ten per cent of case reports from each institution. A senior registrar from HARI visits the institutions and performs audits with institutional registrars present. Audits sometimes turn up information originally be-

lieved to be unavailable.

Accuracy of Information in Case Reports. In preparing a case report, information must be abstracted from source documents and coded, using standard codes for cancer registration. Such information may be abstracted or coded inaccurately, or both. The registry works to minimize reporting errors by educating and supporting institutional registrars, but also seeks to detect and correct errors at all stages of cancer registration.

As newly diagnosed cases of cancer are reported to the RICR, they are visually inspected by experienced registrars for accuracy of coding. A proportion of coding errors are easily spotted by visual inspection and are most efficiently corrected at this stage of registration.

When a coded case report is entered into the computer, a computer program compares each code with an item-specific master code list, rejecting any code which is not found on the list. The program also rejects combinations of codes which have been defined as unacceptable. For example, the program would reject a case in which the gender code indicated "male" and the site code indicated "cervix uteri."

When a senior registrar from HARI visits an institution, at least ten per cent of reports are reabstracted. Errors of abstracting, interpretation, and coding are discovered, discussed, and corrected. Most errors found in this way are errors of abstracting and interpretation.

After case reports have been checked, computerized, and audited by the HARI staff, computer files are transmitted to the RIDH. There they are re-checked for unacceptable codes and code combinations with a computer program which is similar to HARI's but independent of it. Thus far, no errors detectable in this way have slipped through HARI's procedures, but double checking by computer is an inexpensive way to detect errors which may occur when computer programs are altered, or occasionally when computer software or hardware fail.

Omission and Redundancy of Case Reports. No geographical cancer registry has yet been designed which does not omit some cases. Most omissions are avoidable, but some are very costly to avoid. Institutional registrars may inadvertently miss cases diagnosed or treated in their facilities. **Complete** audits of registration at each facility, amounting to independent registration systems, are prohibitively expensive. Some neoplasms, usually *in situ* neoplasms, may be known only to private physicians. Asking **all** private phy-

sicians to make case reports to a geographical cancer registry, an option which requires intensive follow-up, is also prohibitively expensive.

Fortunately, more than one fifth of all cancer patients are diagnosed or treated for cancer in more than one setting. By collecting information from overlapping reporting sources, registries reduce the chance of omitting cases. RICR collects information from hospitals, clinics, private pathology and cytology laboratories, **selected** physician groups, and the cancer registries of Connecticut, Massachusetts, and New Hampshire. The RICR will also obtain some case reports by monitoring death certificates, but this will be useful only when the registry has been run for a longer time.

When information is collected from overlapping reporting sources, redundant case reports are submitted. These must be identified and combined to avoid over-reporting. Before registering a case, RICR compares the report against a master list of registered cases to identify potential redundancies. Multiple personal identifiers (eg, name, date of birth), are used to compensate for inaccuracies in spelling or in numerical information. Later, computerized case reports batched by date of diagnosis are screened for redundancies using multiple personal identifiers. This screening is done partly by computer and partly by hand. The computer does most of the work, but the final decision about a potential redundancy is made by hand after a visual inspection of the data.

As a rough check on over-counted or under-counted cases, RICR computes estimated cancer incidence rates from newly registered cases and compared them with comparable rates from the Connecticut Tumor Registry. Because the historical relationships between Rhode Island's and Connecticut's cancer death rates are known, it is possible to predict, albeit roughly, the relationship which probably exists between the cancer incidence rates of the two states. If the expected relationship between estimated cancer rates is not obtained, additional in-depth analysis may be performed to develop interpretations of the empirical findings. Presently, because of the newness of the RICR, some undercounting of cases in Rhode Island is expected. Connecticut was chosen as a standard against which to compare Rhode Island in this analysis because Connecticut is a contiguous state with known similarities and differences relative to Rhode Island, and because the Connecticut Tumor Registry is "the oldest population-based registry in the world that

Table 1. Number of Composite Case Reports, by Most Informative Reporting Source Available per Report, for Newly Diagnosed Malignant and *In Situ* Neoplasms: Rhode Island, 10/1/86-3/31/87 (Including Resident Cases and Non-Resident Cases)

	Number 10/86-12/86	Number 1/87-3/87	Total 10/86-3/87	Per cent 10/86-3/87
Type of Reporting Source:				
Rhode Island Sources				
Hospital Inpatient	1127	1022	2149	88.5
Clinic	70	94	164	6.8
Laboratory	20	28	48	2.0
Private Practitioner	0	7	7	0.3
Autopsy	6	3	9	0.4
Out-of-State Sources	30	19	49	2.0
Total Composite Reports	1253	1173	2426	100.0

has continuously collected data.”³ Connecticut Tumor Registry data have been demonstrated to be highly reliable.³

Evaluating Early Returns: 10/1/86-3/31/87

Completeness of Information in Case Reports. Over six months, 10/1/86-3/31/87, 2676 individual case reports were made to RICR. From these reports, 2426 composite case reports were constructed. Although ten per cent of individual reports were redundant, they were used to complete information in the composite reports.

Table 1 categorizes 2426 composite case reports by the most informative reporting source available per case. A large majority of case reports, 88.5 per cent, were derived primarily from hospital inpatient records, the most informative source. Another 6.8 per cent were derived primarily from clinic records, a source which frequently contains as much information as hospital inpatient records. Two per cent were derived primarily from reports of the Connecticut Tumor Registry and the Massachusetts Cancer Registry, most of which were derived from hospital inpatient records or from clinic records. Only 2.7 per cent were derived from sources usually characterized by limited information: laboratory records, the records of private practitioners, and autopsy reports. In short, most composite reports were derived from information sources which facilitated the completeness of case reporting.

Table 2 lists the number and proportion of composite case reports for diagnoses made between 10/1/86 and 3/31/87 which contain missing information. Only five of 19 reportable items are missing in as many as five per cent of 2426 case reports. A search of standard tumor registry documents from the American College of Surgeons, the national Surveillance, Epidemiology, and End Results (SEER) system of the National Cancer

Institute (NCI), and the Comprehensive Cancer Centers of the United States (CCUS) failed to reveal standards for the completeness of individual data items in cancer case reports. Nevertheless, it is possible to interpret evaluation results on completeness.

The social security number is missing in 13.6 per cent of composite reports. Some health care facilities do not obtain the social security for their patient records, and therefore do not have it to report to the Registry. Also, a few cancer patients do not have a social security number. It is a useful case identifier, but a case may be properly identified without it, using name, sex, date of birth and address. Absence of the social security number (13.6 per cent of cases) represents an inconvenience, although a minor one, for future registry operations.

The place of diagnosis is missing in 7.0 per cent of composite reports. The place of diagnosis is not necessarily the place from which a cancer case report is made. Some reports are made by facilities in which cancer patients are treated, but not diagnosed. These facilities may not know the place of diagnosis, in which case it cannot be reported. Nevertheless, when place of diagnosis is missing in a composite report, it indicates that the place of diagnosis did not submit a report. This may occur for one of two reasons. First, and more likely, the case may have been diagnosed in a health-care facility which has not been asked to submit case reports. For example, most private physicians' offices have not been asked to do so. Second, and less likely, the case may have been missed by an institutional registrar. A special analysis is being undertaken to determine the plausibility of both explanations.

Stage of disease at diagnosis is missing in 9.2 per cent of composite reports. This figure has been adjusted for cases with unknown primary sites, which cannot be staged. Stage of disease is

Table 2. Number of Composite Case Reports with Missing Information, by Reportable Item, for Newly Diagnosed Cases of Malignant and *In Situ* Neoplasms: Rhode Island, 10/1/86-3/31/87 (Including Resident Cases and Non-Resident Cases)

	Number 10/86-12/86	Number 1/87-3/87	Total 10/86-3/87	Per cent 10/86-3/87
Total Reports	1253	1173	2426	100.0
Reports with No Data on:				
Patient's Name	0	0	0	0.0
Social Security Number	177	154	331	13.6
Address	10	9	19	0.8
Census Tract	10	9	19	0.8
Date of Birth	1	6	7	0.3
Sex	0	1	1	0.0
Race	42	35	77	3.2
Primary Anatomical Site	44	36	80	3.3
Date of Diagnosis	0	0	0	0.0
Place of Diagnosis	69	102	171	7.0
Method of Diagnosis	2	2	4	0.2
Stage of Diagnosis (A)	128	96	224	9.2
Histology	40	30	70	2.9
Behavior	0	0	0	0.0
Grade (B)	485	453	938	38.7
Laterality	58	33	91	3.8
Tumor Sequence Number	0	0	0	0.0
Medical Record Number	53	68	121	5.0
Reporting Facility	0	0	0	0.0

A — Adjusted for cases with unknown primary sites.

B — Adjusted for cases with unknown primary sites, *in situ* cases, leukemias, multiple myelomas, Hodgkin's Disease, and cases for which a histological diagnosis has not been made.

the most important determinant of treatment modality, and therefore should be established in almost all cases with known primary site. Nevertheless, stage is not always established and noted in medical records. A few cases may not be staged because it has been predetermined that treatment is unwarranted or would be detrimental to the patient (usually because of frailty associated with a chronic condition). Finally, information on stage in source documents may be missed by institutional registrars. On the basis of queries and audits, however, it is believed that this is a minor problem.

Stage of disease at diagnosis is a variable commonly used in studies which evaluate early detection and treatment programs. It is an important variable, and when missing from a case report, is largely irreplaceable. Fortunately, other information may be used to classify a tumor as *in situ* or malignant. Although the latter is a crude classification, it is useful in the calculation of incidence rates, which exclude *in situ* tumors.

Tumor grade is missing in 38.7 per cent of composite reports. This figure has been adjusted for cases with unknown primary sites, *in situ* cases, leukemias, multiple myelomas, Hodgkin's disease, and cases for which a histological diagnosis

has not been made. These cases cannot be graded. Theoretically, tumor grade should be available for most other cases. Nevertheless, according to the International Classification of Diseases for Oncology, "The use of grading varies greatly among pathologists throughout the world, and in many instances malignant tumors are not routinely graded."⁴ The RICR collects this information to be consistent with the SEER system. When available, it is not difficult to abstract from medical records. Nevertheless, information on tumor grade is of minor importance to the analysis of registry data in Rhode Island.

The medical record number is missing in 5.0 per cent of composite case reports. On the basis of preliminary analysis, it is believed that most of these cases have not been assigned a medical record number. Rather, their records are filed alphabetically by name. Because personal identifiers and the identity of reporting facilities are available in virtually all cases, the lack of a medical record number in 5.0 per cent of cases is of minor importance.

Accuracy of Information in Case Reports. Table 3 lists the number and proportion of individual case reports for diagnoses made between 10/1/

Table 3. Number of Case Reports with Inaccurately Coded Information, by Reportable Item, for Newly Diagnosed Cases of Malignant and *In Situ* Neoplasms: Rhode Island, 10/1/86-3/31/87 (Including Resident Cases and Non-Resident Cases, and Including All Duplicate Reports)

	Number 10/86-12/86	Number 1/87-3/87	Total 10/86-3/87	Per cent 10/86-3/87
Total Reports (A)	1342	1221	2563	100.0
Primary Site	21	19	40	1.6
Stage	37	25	62	2.4
Histology	55	31	86	3.4
Grade	27	15	42	1.6
Census Tract	24	49	73	2.8
All Other Items (B)	88	38	126	0.5

(A) — Includes duplicate reports for individual cases from different sources.

(B) — Includes all inaccuracies for ten other codable items.

86 and 3/31/87 in which miscoded information was discovered by visual and computer checking. Very little reported information has been miscoded. The greatest proportion of mis-codes was found for histology, 3.4 per cent, followed by census tract, 2.8 per cent, and stage of disease at diagnosis, 2.4 per cent. On the basis of reported information, all other codable items were miscoded in less than two per cent of cases. All mis-codes discovered in visual and computer checks were corrected.

Visual and computer checks of coded information are designed to uncover gross errors. Computer checks identify meaningless codes and meaningless combinations of codes, while visual

checks uncover gross inconsistencies between written descriptions and numerical codes. These gross errors, if left undetected and uncorrected, could severely compromise the registry data set. Sometimes visual checks uncover other inaccuracies as well, but chart audits have been specially designed for this purpose.

Table 4 lists the number and proportion of audited individual case reports for diagnoses made between 10/1/86 and 3/31/87 in which inaccuracies were discovered by re-abstracting case information from the original medical records. Both major and minor discrepancies were found, using definitions established by the registry system of the CCCUS.⁷ In brief, major discrepancies

Table 4. Number of Case Reports with Inaccuracies Discovered through Chart Audits, by Reportable Item, for a Ten Per Cent Sample of Newly Diagnosed Cases of Malignant and *In Situ* Neoplasms: Rhode Island, 10/1/86-3/31/87 (Including Resident Cases and Non-Resident Cases, and Including All Duplicate Reports)

	Major Inaccuracies				CCC Standard (C)
	Number 10/86-12/86	Number 1/87-3/87	Total 10/86-3/87	Per cent 10/86-3/87	
Total Reports (A)	152	128	280	100.0	
Primary Site	8	7	15	5.4	4.0
Stage	29	16	45	16.1	2.0
Histology	13	14	27	9.6	4.0
Census Tract	5	2	7	2.5	4.0
Minor Inaccuracies					
	Minor Inaccuracies				CCC Standard (C)
	Number 10/86-12/86	Number 1/87-3/87	Total 10/86-3/87	Per cent 10/86-3/87	
Total Reports (A)	152	128	280	100.0	
Primary Site	24	20	44	15.7	
Stage	4	2	6	2.1	
Histology	3	7	10	3.6	
Grade	8	3	11	3.9	
All Other Items (B)	36	30	66	2.4	

(A) — Includes duplicate reports for individual cases from different sources.

(B) — Includes all inaccuracies for ten other codable items.

(C) — Standard set by the Comprehensive Cancer Centers of the United States, expressed as maximum acceptable percentage of discrepant cases.

are those which would bias statistics commonly produced from registry data. Minor discrepancies are those which would bias only highly detailed specialized statistics. Major and minor discrepancies have been listed separately in Table 4. Standards for major discrepancies, established by the CCCUS, are also listed in Table 4. The standards are expressed, per item, as maximum acceptable percentage of discrepant cases.

Three codable items were found to have major inaccuracies in four per cent or more audited case reports, namely primary site, stage, and histology. The percentage of cases in which major inaccuracies were found exceeded the standards set by the CCCUS as follows: primary site, 1.4 percentage points; state, 14.1 percentage points; histology, 5.6 percentage points. Census tract coding, inaccurate in only 2.5 per cent of case reports, met the 4.0 per cent standard.

Primary site and stage of disease at diagnosis are very important variables for various uses. Histology, less widely used, is nevertheless important for certain epidemiologic studies. Although the reliability of all three variables must be improved, initial efforts at improvement will be focused on stage of disease at diagnosis, because of the obvious difficulty institutional registrars have had with it.

Omission and Redundancy of Case Reports. Table 5 contains cancer death rates for Rhode Island and Connecticut, providing a perspective from which estimated incidence rates for the two states may be compared. Death rates for the 1950s, 1960s, and 1970s were published by the NCI in collaboration with the Environmental Protection Agency. Rates for the period 1980-1984 were computed from death data published by the National Cancer for Health Statistics and population estimates produced by the two states.

Overall cancer death rates for white males and white females have been consistently higher in Rhode Island since the 1950s, although not by much. In the early 1980s (1980-1984), the cancer death rate for white males was 9.8 per cent higher in Rhode Island than in Connecticut, while that for white females was only 1.4 per cent higher. Death rates from respiratory, digestive, and urinary cancers of white males were 17 to 18 per cent higher in Rhode Island than in Connecticut, while death rates from respiratory, urinary, and breast cancers of white females were virtually identical in the two states. The death rate from digestive cancers of white females was eight per cent higher in Rhode Island than in Connecticut.

Based on these simple comparisons of cancer

death rates in the two states, one would expect higher selected cancer incidence rates for white males in Rhode Island than in Connecticut, and about equal selected cancer incidence rates for white females, (excepting incidence rates for digestive cancers). These rather broad expectations may be compared with observed estimates of cancer incidence rates for the two states, as a crude test of under-count or over-count in the new RICR. It is assumed that the Connecticut Tumor Registry undercounts cases very slightly, based on its long history of high-quality data collection.

Table 6 contains estimated cancer incidence rates for Rhode Island, 10/1/86-3/31/87, and Connecticut, 1/1/86-6/30/86. A confidence interval of two standard errors has been computed for each rate. With one exception, Rhode Island rates are within two standard errors of Connecticut rates. The lung cancer incidence rate for white males is more than two standard errors less in Rhode Island than in Connecticut. Some of the Rhode Island rates exceed the Connecticut rates: colon-rectum and urinary bladder for white males and females. Nevertheless, estimated overall cancer incidence is lower in Rhode Island than in Connecticut, while past cancer mortality would lead us to expect the opposite.

The discrepancy between estimated incidence rates and historical death rates in Rhode Island and Connecticut have a number of plausible explanations. First, Rhode Island may have undercounted new cases of cancer. Notwithstanding other plausible explanations, under-counting in newly established registries is common and should not be discounted as a possibility. Second, known seasonal variations in case reporting may have led to underestimates of annual incidence in Rhode Island and overestimates of annual incidence in Connecticut. Third, population estimates used in the computation of incidence rates may have been incorrect. Finally, the historical relationship between cancer death rates in Rhode Island and Connecticut may have changed. Estimated incidence rates may be harbingers of a future equality in cancer death rates.

Further Analysis Suggested by Evaluation Results

Direct Reporting by Selected Physicians. Few composite case reports were constructed primarily from individual case reports made by private practitioners. Counting reports from the Connecticut Tumor Registry and the Massachusetts Cancer Registry, more than 97 per cent of com-

Table 5. Annual Age-Adjusted (A) Rates of Death from Malignant Neoplasms among Residents, According to Selected Primary Site, Sex, and Race: Rhode Island and Connecticut, 1950s, 1960s, 1970s, 1980-1984

	Rates per 100,000 Population							
	1950s		1960s		1970s		1980-84	
	RI	CT	RI	CT	RI	CT	RI	CT
White Males (B)								
All Sites	208	205	225	212	237	215	236	215
Lung-Bronchus	35	35	54	48	72	61	—	—
Colon-Rectum	38	33	38	31	36	31	—	—
Bladder	9	9	10	9	10	8	—	—
White Females (B)								
All Sites	158	154	145	139	145	140	145	143
Lung-Bronchus	4	6	7	8	15	16	—	—
Colon-Rectum	32	29	29	25	27	22	—	—
Bladder	3	3	2	3	2	2	—	—
Breast	31	30	31	29	31	31	30	30
White Males (C)								
All Sites							236	215
Respiratory							79	67
Digestive							69	59
Urinary							14	12
White Females (C)								
All Sites							145	143
Respiratory							24	25
Digestive							39	36
Urinary							4	4
Breast							30	30

NOTES:

(A) Age-adjusted using the 1970 population of the United States as the standard population, using five year age groups from 0-4 to 85+.

(B) Site groupings defined by the National Cancer Institute:

Lung-Bronchus: ICD-9 162, 163, 165

Colon-Rectum: ICD-9 153, 159.0, 154 except 154.3

Bladder: ICD-9 188, 189.3

Breast: ICD-9 174, 175

(C) Site groupings defined by the National Center for Health Statistics:

Respiratory: ICD-9 160-165

Digestive: ICD-9 150-159

Urinary: ICD-9 188, 189

Breast: ICD-9 174, 175

Sources:

1950s-1970s:

U.S. Environmental Protection Agency and National Cancer Institute: Cancer Mortality Rates and Trends, 1950-1979. U.S. Government Printing Office, Washington, 1983.

1980s: Computations based on data from:

National Center for Health Statistics: Vital Statistics of the United States, 1980-1984, Vol. II, Mortality, Part B. Public Health Service, Washington. U.S. Government Printing Office, 1985-1987.

Bureau of the Census: 1980 Census of Population, Vol. 1, Characteristics of the Population, Chapter B. General Population Characteristics. U.S. Government Printing Office, 1982.

posite case reports drew information from hospital inpatient records or clinic records, both of which are very informative sources of registry information. In contrast, 0.3 per cent drew information primarily from the records of primary care physicians. These seven case reports were obtained at significant expense. Every dermatologist, ophthalmologist, urologist, and gynecologist in Rhode Island was approached to obtain information on selected cases of melanoma, cancer of the prostate, or cancer of the cervix uteri. Overall, 40 individual case reports were

received after repeated mailings and queries. Of 40 case reports, 33 were redundant and only seven cases would have been missed had these physicians not been contacted. These findings and other relevant information will be assessed to determine whether or not selected physicians will be asked to report directly to the registry in the future.

Place of Diagnosis. Missing information on place of diagnosis will be investigated further. The findings thus far suggest that certain case reports may not have been submitted to the registry.

Table 6. Estimated Annual Age-Adjusted (A) Incidence Rates of Malignant Neoplasms among Residents, According to Selected Primary Site, Sex, and Race: Rhode Island, 10/1/86-3/31/87; Connecticut, 1/1/86-6/30/86

	Rates per 100,000 Population Rhode Island	Rates per 100,000 Population Connecticut
White Males		
All Primary Sites	376.4 ± 26.2 (B)	390.3 ± 14.8
Lung	63.3 ± 10.8	76.6 ± 6.6
Colon-Rectum	69.9 ± 11.3	67.3 ± 6.2
Urinary Bladder	33.4 ± 7.8	28.2 ± 4.0
White Females		
All Primary Sites	310.0 ± 22.7	319.6 ± 13.0
Lung	31.7 ± 7.3	34.5 ± 4.3
Colon-Rectum	48.2 ± 9.0	42.3 ± 4.7
Urinary Bladder	8.6 ± 3.8	7.2 ± 2.0
Breast	96.3 ± 12.7	102.1 ± 7.3

(A) Age-adjusted using the 1970 population of the United States as the standard population, using five year age groups from 0-4 to 85+.

(B) Two-standard-error confidence intervals.

Sources:

Rhode Island: Rhode Island Cancer Registry data base.

Connecticut: Connecticut Tumor Registry

Analysis will focus on identifying those health care facilities (places of diagnosis) which have not made reports. Many of these will probably be identified as private physicians' offices. With a few exceptions, physicians have not been asked to report to the registry, because most patients diagnosed as having malignant neoplasms are treated as inpatients or outpatients at acute care hospitals, all of which are reporting. However, some of the health care facilities identified in the analysis may be among those which have been asked to report to the registry. Efforts will be made to improve case findings at these facilities.

Tumor Grade. Information collected by the RICR on case identification, demographics, and diagnosis are designed to be compatible with the SEER system. Tumor grade is one of these items of information. Evidently, tumor grade is not systematically noted in pathology reports.⁴ This problem has recently become the subject of review by the Cancer Committee of the College of American Pathologists: "The committee will focus its efforts on guidelines for grading, which will then become the subject of educational programs for all pathologists."⁵ When tumor grade is noted, it is easy to abstract and code. Further evaluation of this variable will be made to determine if the Rhode Island experience is similar to the experience of SEER registries, or if practices unique to Rhode Island are responsible for the

high proportion of composite case reports in which tumor grade is missing.

Activities Suggested by Evaluation Results

Changes in Computer Software. As data analysis proceeded, registry software was altered or added to answer specific evaluation questions. In so doing, software errors were found and corrected, and the efficiency of particular software modules was increased. Inconsistencies between the software packages of HARI and of RIDH were identified and corrected. Other changes have been suggested to enhance quality assurance checks, and these will be undertaken.

Focused Educational Sessions. The results of chart audits have been analyzed in greater detail than the summary statistics presented in Tables 3 and 4. Against a background of apparently random error, patterns of mis-codes emerged which suggest the need for specific coding workshops. Two workshops are planned in the coming year, each of which will include two modules: First, specific coding problems will be addressed in a lecture followed by illustrative coding exercises. Coding stage of disease at diagnosis will be emphasized. Second, following the practice of the CCCUS, registrars will abstract and code a set of test cases ("prepared from actual charts, chosen from the most common anatomic sites") to determine the inter-coder reliability and stimulate discussion on a wide range of coding topics. A panel of senior registrars will discuss questions about coding. The CCCUS use test cases as an adjunct to chart audits for evaluating the reliability of coding. The two techniques have complementary strengths. It is hoped that by implementing test case modules certain coding problems may be identified and solved when institutional registrars are assembled *en masse*.

The Adequacy of Registry Data for Specific Uses

Computation of Incidence Rates. The registry data are sufficiently complete to compute significant overall incidence rates when twelve months' data have been collected and edited. Overall incidence rates will underestimate the true incidence of cancer in Rhode Island, but only slightly. This warning will be published with the rates. If possible, the extent and characteristics of undercount will be estimated. Also, all incidence rates will be published with confidence limits because of the random variations which may occur from year to year in small incidence rates.

The registry data are adequately specific to compute incidence rates by primary anatomical

site, when twelve months' data have been collected and edited. A very small proportion of cases are missing information on primary site.

Evaluation of Screening Programs. The evaluation of screening programs requires reliable information on stage of disease at diagnosis, because an important screening objective is to increase the proportion of cases diagnosed at earlier stages of disease. The proportion of un-staged and mis-staged composite cases varies among primary anatomical sites, but on average exceeds ten per cent. The completeness and reliability of information on stage must be improved before registry data are used to evaluate screening programs.

One unknown factor in the evaluation of screening programs is the reliability of registry data for *in situ* cases. The *in situ* stage is the earliest stage at which true cancers are detected and therefore takes on importance for the evaluation of early detection. *In situ* cases are excluded from the computation of incidence rates, because the number of *in situ* cases diagnosed in a particular population depends strongly on the extent of effective screening programs. The number of *in situ* cases registered also depends on the settings in which these cases are diagnosed and treated, and whether these settings have been asked to report regularly to the registry. Some *in situ* cancers, unlike most malignant cancers, are diagnosed and treated appropriately in the offices of private practitioners. In short, under-count or over-count of *in situ* cases is difficult to evaluate. The use of *in situ* cases in evaluation will require careful preliminary analysis of trends in the number and proportion of these cases over a period of time.

Geographic Surveillance. The registry data are sufficiently complete for geographical surveillance. Less than one per cent of composite cases are missing geographic codes (census tracts and zip codes). However, data will have to be aggregated for a number of years to produce reliable incidence rates or ratios for towns or smaller geographical areas. Twelve months' data will be barely adequate to compute county rates.

Basis for Epidemiologic Studies. In addition to the completeness and reliability of data, the timeliness of data collection is important to those epidemiologic studies which require interviews with the cancer patients. Thus far, registry data have been available in quarterly batches (checked visually and by computer, and corrected) nine months from the end of the quarter in which the cases were diagnosed. Unedited data have been

largely available in quarterly batches six months from the end of the quarter in which the cases were diagnosed. This schedule should be adequate for some epidemiologic studies, while others requiring faster case identification should be facilitated by the existence of the registry system.

Conclusions

Composite case reports are largely complete and accurate, but three key variables do not meet reliability standards set by the CCCUS. The RICR may be under-counting cases, but only slightly, based on a comparison of Rhode Island and Connecticut cancer data. Registry data may be used in the computation of incidence rates, geographic surveillance, and some epidemiologic studies. On the basis of evaluation results, registrars' workshops have been designed to enhance the reliability of registry data, with a special focus on stage of disease at diagnosis. When the reliability of this variable is improved, registry data will also be useful in the evaluation of screening programs.

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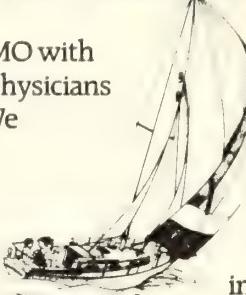
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A Commencement Address

Levi C. Adams

The Class of 1988 is a very special class to me. Over the past four years, and for a number of you seven or eight years, we have shared concerns about public health policy, health services to the disadvantaged, access to health manpower training, and the stresses and rewards of preparing to pursue a career as a physician or a medical scientist.

I have appreciated having the opportunity to try to help some of you to understand some of these issues better, and to assist you in setting agendas for your service or research as students now or for your careers in the years ahead. So I am honored that you have chosen me to represent the medical faculty and administration in this special ceremony which is at once an ending and a beginning.

It is the beginning of your transition from student to teacher, from follower to leader, from borrower to payer, and from active questioner to alert investigator. It is the setting of the sun on the role of this faculty as professor and the dawning of the new day when you are embraced as 82 new colleagues. It is a beginning and an end.

Mr. Adams is Associate Vice President for External Affairs with the Division of Biology and Medicine, Brown University, Providence, Rhode Island.

Delivered on May 30, 1988, at the Commencement of the MD Class of 1988. Brown University, Providence, Rhode Island, at the First Unitarian Church.

As I look out on your bright faces and see you bedecked in the regalia of the ritual of the academy, I am reminded of the night of the high school prom, when the child who is about to become an adult enters the living room or parlor in anxious anticipation, awaiting answers to the unspoken questions: "How do I look?" "Am I ready?" but also awaiting with impudent impatience the inevitable final admonitions and instructions that the parents feel obliged to give. And so it is my lot to respond to your questions and to give a final exhortation on a few things for you to consider as you spring forth on the world as new physicians.

How do you look? You look great! We see in your eyes the confidence that you have gained enough knowledge to be entrusted with the lives of others. And this pleases us. And we say this is good. But we also see on your countenances just enough fear to keep your adrenalin flowing and keep you alert to the possibility of the unpredictable. And this pleases us more. And we say that this is good.

You look just super! As you stand, tall, yet not imposing; proud, and yet humble; excited, and yet serene that you — like Hippocrates and Imhotep, great physicians of another time — have been chosen, endowed, nurtured, protected, provided for, and now challenged to discharge your lives with usefulness and reputation. And from your resonant voices of strength we hear each of you say: "I accept the challenge! I am ready!" And this pleases us. And we say this is good.

Yes, you are ready. When we shake your hands

and embrace you, we feel the firmness that will fix broken bones and failing eyesight. We feel the solid skill that will replace worn out kidneys and tobacco-destroyed lungs. We feel the warmth that will bring new life and new hope into our world. And this pleases us. And we say this is good. When we touch you, we also feel the gentleness that will console those who grieve, calm those with fear and anxiety, and reassure those who distrust and doubt. And this pleases us more. And we say this is good.

Yes, you are ready, for we have seen the growth of your intellectual curiosity. We are confident that somewhere along your path dread diseases like AIDS and schistosomiasis will yield to your scholarly tenacity. We have seen you reach out across the world to the tired in Central America and in Central Mississippi, to the poor and the hungry in Tanzania and in Texas, and to the homeless in the Middle East and in mid-Manhattan. And we know that, if you hold on to what you have, the world tomorrow will be better than the world today. And this pleases us. And we say this is good.

Yes, we know you are ready, because we have witnessed your skills, we have seen your compassion for others, we, like proud parents, have watched you care for one another, and we have seen your tears. Sometimes tears of joy when you realized how privileged you are to have been given so much — parents and loved ones who gave of themselves so that you might have access to the pot of gold at the end of the rainbow; teachers and classmates who dared you, challenged you, tutored you and who patiently encouraged you to believe that there was a light at the end of the tunnel, even though you stood in utter darkness; and the God of the universe who blessed you with the mental and physical wherewithal to enter this marathon and to endure until the finish line is in view. Yes, we have seen your tears of joy, and we are pleased and say that this is good. But we have also seen your tears of sadness. You wept at the death of a grandparent, a parent, a classmate, and a friend who could not be here for the whole journey. And as you wept we saw a deepening determination to succeed as a tribute to those you mourned. We saw your tears of sadness when you witnessed the unnecessary and preventable loss of life that we see almost daily. And we saw your tears of apprehension when you comprehended the enormity of the responsibility that goes with your privilege. We saw your tears and were pleased, and we said this is good.

You are ready, and all the Brown Family takes

pride in your accomplishments. From Louie Periera to Steve Smith, from Bettye Williams to Pierre Galletti, from Cindy Kern to Paul Calabresi, from Howard Swearer to Lenny Erickson. You have done us proud. We are pleased to have played a role in making this day possible. We have come this final time to pay tribute to your accomplishments, to bid you Godspeed, and to give the obligatory final admonitions.

I am informed by Dean Greer that all commencement talks have to have a formal title in order to be preserved properly in the annals of the University. Therefore, in the best Baptist tradition that one can muster here in this Unitarian Church, I invite you to think along with me for a few more minutes on the topic: *The Challenge of Medicine: The Joy of Life*.

As I travel around the nation, it is impressive to me that so many medical students and house officers seem to be having second thoughts about whether becoming a physician is a blessing or a burden. Whether the journey, that was started so long ago, was to a place along a yellow brick road that has somehow vanished and been replaced by something much more foreboding. It troubles me that the growing preoccupation of some of your teachers with the problems of Diagnosis Related Groups (DRGs), liability insurance, licensure and relicensure requirements, and fears of the broadening applications of sophisticated technology to medical practice may have distorted the reality that you, as practitioners of the science of preventing disease and the art of healing, still are part of the noblest profession on earth — and as such have the potential for receiving and giving great joy.

As you and those whom you serve rejoice, you will reinforce or rediscover the dreams of your early years. You will understand that joy is the essence of life and that the mission of medicine and medical sciences is *life* — not existence, *but life*; not absence of illness; *but life*; not tolerance for pain or palliation, *but life*. The Challenge of Medicine is the Joy of Life.

Please don't misunderstand. The concerns of today's physicians are about real problems, but they can't stop you from feeling good when the grateful patients says "Thank you, Doctor, for saving my life." They can't take away from you the rush of satisfaction you get when you are introduced by your mother as "my daughter or my son the doctor," and you reflect on what that means and what you've been through to earn that appellation. Or even take away from the assurance that you get in those desolate times when

you know that you have done all that you can and your patient dies. And just when you are feeling low, inept, and inadequate, some mourning member of that family comes to thank you for your sensitivity, compassion, and skill.

The concerns about today's medicine are obstacles to overcome, mountains to climb, and rivers to ford. But they will never be burdens to arrest you, if you keep your heart and your mind on your dream — the dream that life can be beautiful if you rise every morning with your receptors programmed for joy, programmed for life. The Challenge of Medicine is the Joy of Life.

In the context of being prepared to give joy and to gain joy, there are four characteristics that you should cultivate and make an integral part of your professional and your personal lives. This is your final lesson, so let me give you a little memory aid. Let's call these characteristics the Four L's. They are (1) Laughing, (2) Listening, (3) Learning, and (4) Loving. These seem like fairly simple things to make part of your life; but be warned, experience has taught us that many physicians have difficulty displaying skill in all of these areas.

Laughing. Let's take **Laughing**, and its precursor smiling, as instruments of joy, and in turn conduits of life. While medicine is surely serious business, be mindful not to take yourself too seriously. There is a great danger that, if you do take yourself too seriously, you will be swept away with concern for the form and fashion of medicine, rather than its substance. So laugh for yourself. *Laugh for your patient.* I believe that it is therapeutic for a patient to be relaxed. If your face mirrors the tensions and anxieties the patient has, it seems likely that these tensions will mount and provide less than the optimum environment for healing. It seems likely that they will delay the evolution of the partnership that is needed between you and the patient or the patient's family in order to get the most from your knowledge. So laugh a little, or at least smile, for your patient. *Laugh for your family:* Too often physicians forget that the bond within family requires the doctor member to be an equal. To descend from a lofty perch and show that physician is not God, but human, not untouchable, but a tangible being with feelings of joy, sorrow, pleasure, and pain. One who makes errors and sometimes forgets, but one who can laugh at oneself or smile the smile which invites the child or the spouse or another loved one to come inside to be part of your life, enhancing the joy in the good times and reinforcing a bridge over trou-

bled waters when you are caught in despair. Too many physicians' families have been unable to stay the course because they saw no opportunity to share the joy. Extend this concept to your friends, your colleagues, your secretary, the charge nurse, and all who are in your life, and your life will be richer and the lives around you more joyful. The Challenge of Medicine is the Joy of Life. Promise yourself that you will laugh sometimes (often) with your family, friends, colleagues, and even with strangers.

Listening. I am sure that you have had frequent instruction about listening to your patient. But I invite you to review all your notes on listening and regularly examine yourself to see if your practice matches your knowledge. Sometimes, the words that are spoken mask the words that are in the patient's mind. If you don't hear these hidden words, you will be less a doctor than you ought to be. Sometimes, you will be just so anxious to share your vast knowledge that you will be thinking about your reply even as the patient is talking. In doing so, you fail to hear that the chief complaint is not the chief complaint at all. And you miss an opportunity to be the doctor that you might be, and your patient misses an opportunity for joy, for life. I admonish you to listen to your patients.

I also admonish you to listen to your children, to your spouse, to your friends, and to your colleagues. Listening is the first sign of caring. When people think you don't care, there is an emptiness and a sense of being abandoned. And in the profession of medicine we have seen too much suicide, too much alcoholism, too much narcotic addiction, and too many broken families not to realize that some who cried out were not heard, and having no voice they lost the will to live, and they lost the joy of living. It's in your hands to know that the Challenge of Medicine is the Joy of Life, and listening, truly listening is life giving.

Learning. If there is one lesson I want to give you, it is that, with all that you have learned, you know so little of what there is to know. Every human being, and especially every physician, must be committed to a lifetime of learning. The more you know, the better doctors, parents, friends, parishioners, teachers, neighbors, and spouses you will be. Your classroom must be wherever you are. Your teacher, whoever is with you. You can learn a lot from a plumber, or a gardener, or a neighborhood child. Learning from others is respecting others. Respect brings joy and Joy is Life.

Loving. Finally, life is about love. Teach your-



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self to love life itself, and you will unfold before you the pages that enscript how you should live. Look and see those about you who need not only your skills as a physician, but your caring concern as a citizen, your dreams as a parent and spouse, your devotion as a friend.

It is love that is needed to conquer hate. It is love that gives health the victory over disease, makes peace conqueror of war, and provides homes for the homeless and freedom for those who are imprisoned in poverty, prejudice, and ignorance.

As you go down from College Hill to the promising world of tomorrow, we wish you love, we wish you joy, we wish you life. Go and be well.

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Please see references and summary of product information on following page.



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Before prescribing, please consult complete product information, a summary of which follows.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides, documented megaloblastic anemia due to folate deficiency, pregnancy at term and during the nursing period; infants less than two months of age.

WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.

BACTRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice, may be early indications of serious reactions. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Perform complete blood counts frequently.

BACTRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillpharyngitis have a greater incidence of bacteriologic failure when treated with Bactrim than with penicillin.

PRECAUTIONS: General: Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (e.g., elderly, chronic alcoholics, patients on anticonvulsants, with malabsorption syndrome, or in malnutrition states) and severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur, frequently dose-related.

Use in the Elderly: May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, e.g., impaired kidney and/or liver function, concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly. In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura has been reported. Make appropriate dosage adjustments for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION).

Use in the treatment of Pneumocystis Carinii Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS): AIDS patients may not tolerate or respond to Bactrim in same manner as non-AIDS patients. Incidence of side effects, particularly rash, fever, leukopenia, elevated aminotransferase (transaminase) values, with Bactrim in AIDS patients treated for *Pneumocystis carinii* pneumonia reported to be greatly increased compared with incidence normally associated with Bactrim in non-AIDS patients.

Information for Patients: Instruct patients to maintain adequate fluid intake to prevent crystalluria and stone formation.

Laboratory Tests: Perform complete blood counts frequently; if a significant reduction in the count of any formed blood element is noted, discontinue Bactrim. Perform urinalyses with careful microscopic examination and renal function tests during therapy, particularly for patients with impaired renal function.

Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. Keep this in mind when Bactrim is given to patients already on anticoagulant therapy and reassess coagulation time. Bactrim may inhibit the hepatic metabolism of phenytoin. Given at a common clinical dosage, it increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When giving these drugs concurrently, be alert for possible excessive phenytoin effect. Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

Drug/Laboratory Test Interactions: Bactrim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs if methotrexate is measured by a radioimmunoassay (RIA). The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis. Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim. Mutagenesis. Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination, concentrations used exceeded blood levels of these compounds following therapy with Bactrim. Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities. Impairment of Fertility. No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

Pregnancy: Teratogenic Effects. Pregnancy Category C. Trimethoprim and sulfamethoxazole may interfere with folic acid metabolism; use during pregnancy only if potential benefit justifies potential risk to fetus. Nonteratogenic Effects. See CONTRAINDICATIONS section.

Nursing Mothers: See CONTRAINDICATIONS section.

Pediatric Use: Not recommended for infants under two months (see INDICATIONS and CONTRAINDICATIONS sections).

ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION).** **Hematologic:** Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia. **Allergic Reactions:** Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. Periorbital nodosa and systemic lupus erythematosus have been reported. **Gastrointestinal:** Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia. **Genitourinary:** Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria. **Neurology:** Aspiric meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. **Psychiatric:** Hallucinations, depression, apathy, nervousness. **Endocrine:** Sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents; cross-sensitivity may exist. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. **Respiratory:** Pulmonary infiltrates. **Musculoskeletal:** Arthralgia, myalgia. **Miscellaneous:** Weakness, fatigue, insomnia.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITS MEDIA IN CHILDREN: Usual adult dosage for urinary tract infections is one DS tablet, two tablets or four teaspoonsful (20 ml) b.i.d. for 10 to 14 days. Use identical daily dosage for 5 days for shigellosis. Recommended dosage for children with urinary tract infections or acute otitis media is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses every 12 hours for 10 days. Use identical daily dosage for 5 days for shigellosis. **Renal Impaired:** Creatinine clearance above 30 ml/min, give usual dosage, 15-30 ml/min, give one-half the usual regimen, below 15 ml/min, use not recommended.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS: Usual adult dosage is one DS tablet, two tablets or four teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONIA: Recommended dosage is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

HOW SUPPLIED: DS (double strength) Tablets (160 mg trimethoprim and 800 mg sulfamethoxazole)—bottles of 100, 250 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20. Tablets (80 mg trimethoprim and 400 mg sulfamethoxazole)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40. Pediatric Suspension (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 100 ml and 16 oz (1 pint). Suspension (40 mg trimethoprim and 200 mg sulfamethoxazole per teasp.)—bottles of 16 oz (1 pint).

STORE TABLETS AT 15°-30°C (59°-86°F) IN A DRY PLACE PROTECTED FROM LIGHT. STORE SUSPENSIONS AT 15°-30°C (59°-86°F) PROTECTED FROM LIGHT.

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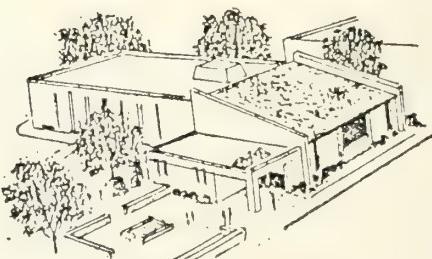
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AMA Report of the Board of Trustees

Organ Procurement System

Resolution 125, which was adopted by the House of Delegates at the 1987 Interim Meeting, called upon the AMA to (1) study the issue of donor procurement in the context of new required laws and federal legislation, and (2) include recommendations regarding the role physicians and other personnel should assume in organ procurement and the criteria that should be included in organ procurement protocol. This report is submitted for the information of the House of Delegates.

Introduction

In Report Y of the Board of Trustees filed at the 1987 Interim Meeting, the Board updated information for the House on the current status of organ procurement in the United States. As indicated in Report Y and in Resolution 125, the availability of organs is often the most limiting factor in a physician's ability to deliver effective treatment to patients in need of an organ transplantation procedure. In 1986, there were approximately 10,000 kidneys, 1,400 hearts, 40 heart/lungs, 900 livers, 130 pancreata, 28,000 corneas, and 1,160 bone marrows transplanted in the United States. Despite the growing numbers of transplants, approximately 9,000 patients are waiting for donor kidneys, 5,000 for corneas, 300 for livers, and 300 for hearts.

The life or death situation facing these patients

At the Annual Meeting of the AMA House of Delegates, June 26-30, 1988, in Chicago, action was taken to direct the Department of Technology Assessment to analyze organ procurement protocols developed by hospitals and find out what problems physicians encounter in implementing required request laws.

and the present scarcity of available organs necessitate the most effective and efficient utilization of present resources and an increase in efforts to enhance the supply of available organs. By enactment of required request laws for organ transplantation, 43 states and the District of Columbia have sought to increase the number of available organs. These laws vary somewhat among the states, but all require hospitals and hospital personnel routinely to provide patients and/or families with the opportunity to authorize a donation.

On March 31, 1988, the federal government implemented a requirement that hospitals, as a condition of participation in Medicare and Medicaid programs, have written protocols to identify potential organ donors. These laws and regulations are aimed at rectifying the present situation in which there often is either no consideration of donation or no definitive decision on organ donation. These circumstances annually pertain to 19,000 potential donors (70 per cent of all potential donors).

Impact of Required Request

In 1985, Oregon, California, and New York became the first states to pass required request laws. Following implementation of these laws, Stanford Medical Center has experienced a 38 per cent increase in heart and heart/lung donations, New York has had a 48 per cent increase in all organ and tissue donations, and Oregon has observed an increase in tissue donations (134 per cent for cornea).

The Division of Organ Transplantation of the Department of Health and Human Services (HHS) has commissioned a study to assess the impact of state required request laws on organ

procurement and to identify problems and concerns that have arisen. Preliminary results indicate that state required request laws do have a positive effect on organ and tissue donation. This effect primarily may be due to the fact that such laws enhance the public's familiarity with and awareness of organ and tissue donation. This study, which is being conducted by a private contractor, is scheduled for completion in 1988.

Primary Role of Physicians

The role of physicians primarily involved in the care of patients and thus of potential organ donors is not well defined either by explicit law or regulation. In fact, in most statutes or required request sections of Uniform Anatomical Gift Acts, the physician is not mentioned. In caring for a terminally ill patient, the physician's obligation to meet the medical and social needs of his/her patient potentially conflicts with the responsibility to identify individuals who are suitable candidates for organ donation.

The Council on Ethical and Judicial Affairs (CEJA) has provided its position on the role of physicians in organ transplantation (Current Opinions, Section 2.15):

- (1) In all professional relationships between a physician and his patient, the physician's primary concern must be the health of his patient. He owes the patient his primary allegiance. This concern and allegiance must be preserved in all medical procedures, including those which involve the transplantation of an organ from one person to another where both the donor and recipient are patients. Care must, therefore, be taken to protect the rights of both the donor and the recipient, and no physician may assume the responsibility in organ transplantation unless the rights of both donor and recipient are equally protected.
- (2) A prospective organ transplant offers no justification for a relaxation of the usual standards of medical care. The physician should provide his patient, who may be a prospective organ donor, with that care usually given others being treated for a similar injury or disease.
- (3) When a vital, single organ is to be transplanted, the death of the donor shall have been determined by at least one physician other than the recipient's physician. Death shall be determined by the clinical judgment of the physician. In making this determination, the ethical physician will use currently

- accepted and available scientific tests.
- (4) Full discussion of the proposed procedure with the donor and the recipient or their responsible relatives or representatives is mandatory. The physician should be objective in discussing the procedure, in disclosing known risks and possible hazards, and in advising of the alternative procedures available. The physicians should not encourage expectations beyond those which the circumstances justify. The physician's interest in advancing scientific knowledge must always be secondary to his primary concern for the patient.
- (5) Transplant procedures of body organs should be undertaken (a) only by physicians who possess special medical knowledge and technical competence developed through special training, study, and laboratory experience and practice, and (b) in medical institutions with facilities adequate to protect the health and well-being of the parties to the procedure.
- (6) Transplantation of body organs should be undertaken only after careful evaluation of the availability and effectiveness of other possible therapy.

Notwithstanding this opinion, more issues^{1,2} regarding the specific role of the primary physician may persist. For the primary attending physician, the issues revolve around the identification of donors, actual process for request of organ donation, maintenance of medical records, and determination of death.

As mentioned above, the attending physician plays a key role in identifying potential donors. Physicians should familiarize themselves with the general inclusion and exclusion criteria for eligibility for organ and tissue donation. In identifying a potential donor, the attending physician should consult with appropriate members of the transplant program about criteria for a patient's medical eligibility. This should diminish the occurrence of requests for donation from patients later determined to be unacceptable donors. Also, the religious preference and convictions of patient and next of kin should be considered and respected.

In the actual request process, most hospitals have designated an individual trained as a requestor to make the actual request for organ donation. The attending physician, however, will generally introduce the subject of organ donation to the patient and/or next of kin. The physician also will introduce the individual who for-

mally will make the request. All through this process, the primary physician should provide support to the patient, next of kin, and eventually, the survivors.

Maintenance of a comprehensive medical record detailing the condition, interventions, and circumstances of death is critically important for all patients. In cases of potential organ donation, however, detailed clinical information about the donor and information on the disposition of the next of kin toward donation can facilitate the organ retrieval and matching processes.

The determination of brain death is a vital criterion of any required request program. The determination of death, as discussed in the CEJA opinion, is to be based upon the clinical judgment of the primary physician in consultation with neurologic or neurosurgical specialists. Each hospital should have established a brain death protocol. The medical criteria for determination of brain death should be established and approved by appropriate members of the hospital medical staff. The physician pronouncing death should complete the death certificate, except in those instances in which the medical examiner, coroner, or justice of the peace has jurisdiction.

The focus of this report has been on the time of death mechanism for required request. The federal statute and most, if not all, state laws mandate this form of request. In November 1987, however, the National Conference of Commissioners on Uniform State Laws recommended that all 50 states amend their Uniform Anatomical Gift Acts to require an admission mechanism of required request. This amendment would require that on or before admission to a hospital each patient who is a potential donor must be informed about organ donation and asked about their willingness to donate. Concern about this potential requirement has been voiced by some members of the transplant community. It is clearly an issue that requires more in depth consideration before widespread enactment.

Conclusion

This preliminary analysis on the effect of state required request laws on practicing physicians indicates a general acceptance of the mandate enacted by state legislatures. No major concerns have been identified at this time. Whether this acceptance reflects concurrence with the overriding importance of improving organ procurement and availability, appropriate granting of flexibility and discretion to local institutions or a general low level of involvement by physicians

(either by active or passive decision) in the implementation of required request laws has not been explicitly examined in this analysis. The impact of federally mandated required request is indeterminate because the regulations have not been implemented as of this writing. Assessment of the impact of state required request laws and identification of problems attending the implementation of these laws should be provided by the study of the Division of Organ Transplantation of HHS, which is nearing completion.

The Board will closely monitor implementation of federally mandated required request and will evaluate the study on the impact of state required request laws. Moreover, in the interest of assuring the appropriate role and involvement of practicing physicians in organ procurement, the AMA, through the Department of Technology Assessment, will conduct a two-part survey to:

1. analyze the types of written protocols developed by hospitals and the roles that physicians played in developing, implementing, and carrying out such protocols; and
2. ascertain directly from physicians those issues, concerns, and problems that attend the implementation of required request.

The Board will ask the Council on Scientific Affairs to review the clinical issues inherent in the "Guidelines for Hospital Administration for Implementing Required Request" developed by the American Council on Transplantation (ACT). The Board then will take action to rectify any inequities or inadequacies identified by these studies. The Board also will continue to work with organizations such as the American Council on Transplantation, the American Hospital Association, the United Network for Organ Sharing, and appropriate medical specialty societies to improve our nation's system for organ procurement and transplantation.

The Board will issue a final report detailing the results of its activities, surveys, and analysis of the federal study on required request laws at the 1988 Interim Meeting of the House. Finally, the Board reaffirms its position that practicing physicians should do all they can to enhance the pool of available organs, a national resource and a reservoir of life.

References

- ¹ American Council on Transplantation: Guidelines for Hospital Administration for Implementing Required Request. December, 1987.
- ² Toile SW, Bennett WM, Hickam DM, et al.: Responsibilities of Primary Physicians in Organ Donation. *Ann Int Med* 1987;106:740-744.

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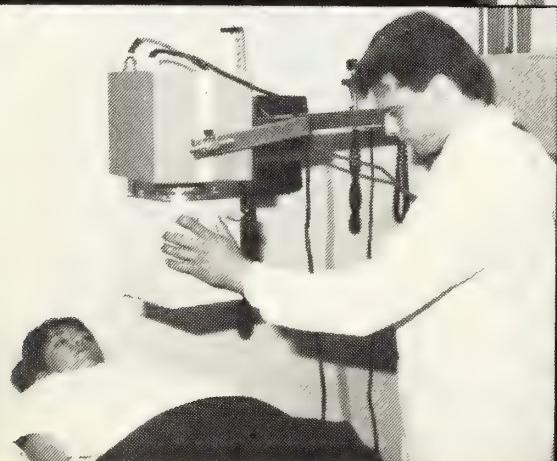
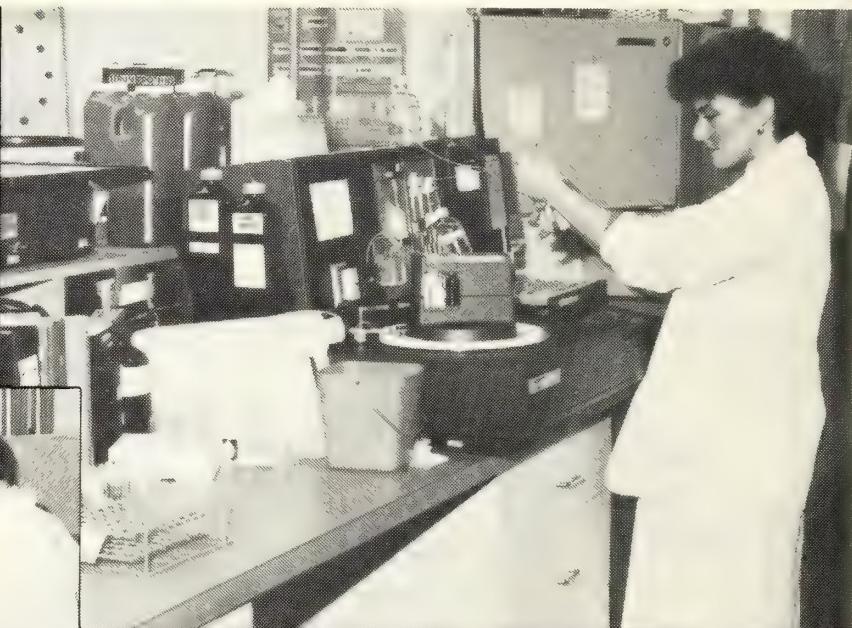
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PERIPATETICS

Author of one of the key chapters of the recently published Surgeon General's annual report on smoking was **Dr David B. Abrams**, associate professor of psychiatry and human behavior at Brown and Miriam Hospital. **Dr Abrams** was a chief spokesman on behalf of the report at a recently held State Health Department press conference.

• • •

The Medical Staff Association of The Miriam Hospital recently elected new officers at its annual meeting on June 8. They include **Dr Frederick S. Crisafulli**, President; **Dr Charles B. Kahn**, Vice President; **Dr Stephan Deutsch**, Secretary; **Dr Steven Cohen**, Treasurer; **Dr David Kitzes**, Member at Large (2 years); **Dr James McCartney**, Member at Large (2 years); and **Dr Stanley Simon**, Emeritus Member.

• • •

The Society for Cardiovascular and Interventional Radiology recently elected **Dr Gary S. Dorfman**, clinical associate professor of medicine at Brown and Rhode Island Hospital, to fellowship.

• • •

Dr Stephen Kaplan, professor and associate dean of medicine at Brown, has been elected to the Education Council of the American Rheumatism Association. **Dr Kaplan** will also serve on an Arthritis Foundation Task Force.

• • •

The Institute of Medicine, National Academy of Sciences, in Washington, DC, elected **Dr Charles C. J. Carpenter**, physician-in-chief at The Miriam Hospital, to membership. **Dr Carpenter** will work on behalf of the organization and the studies it produces.

• • •

Vice President for Biology & Medicine at Brown University, **Dr Pierre M. Galletti** was presented

The William Williams Keen Award at the Brown Medical Alumni Association's Fifteenth Annual Commencement Banquet on May 29, 1988.

• • •

The National Vaccine Advisory Committee of the National Vaccine Program has invited **Dr Georges Peter**, professor of pediatrics at Brown and Rhode Island Hospital, to serve a two year term by the United States Department of Health & Human Services.

• • •

Dr Steven A. Wartman, associate professor of medicine at Brown University and physician-in-chief, division of general internal medicine at Rhode Island Hospital, has been elected president of the Society of General Internal Medicine.

• • •

South County Hospital has recently appointed **Dr Allen V. Hurt**, a specialist in plastic surgery, to its medical staff.

• • •

The American Academy of Orthopedic Surgeons (AAOS) recently elected **Dr John M. Roberts**, surgeon-in-chief, Division of Pediatric Orthopedics at Rhode Island Hospital, to the Board of Directors at its 55th annual meeting in Atlanta. **Dr Roberts** is also acting chairman of the Department of Orthopedics and Rehabilitation at Rhode Island Hospital, a consultant to the medical staff at Women and Infants Hospital, and professor in the Departments of Orthopedics and Pediatrics at Brown University.

• • •

Associate Dean of Medicine at Brown University, **Dr Stephen R. Smith** was recently appointed chairman of the National Board of Medical Examiner's Part II Committee 2 Test Committee. The responsibilities include development of National Board Examinations and assuring the quality and integrity of the overall evaluation system of the National Board of Medical Examiners.

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Good, clear communication about medicines can increase compliance, prevent problems, and lead to better health.

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Information for Authors

Manuscripts: Manuscripts will be accepted for consideration with the understanding that they are original contributions, have never been published or submitted elsewhere, and are submitted only to the *Rhode Island Medical Journal*.

Specifications: Manuscripts must be original typed copy (not all capitals) on 8½x11 inch firm typewriter paper, double-spaced (including the text, case reports, legends, tables, and references) with 1½ inch margins. Carbon copies will not be accepted. Subheadings must be inserted at reasonable intervals to break the typographic monotony of the text. Pages must be numbered consecutively. Italics and boldface print are never used except as subheadings.

Abbreviations: The *Journal* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

Title page: All manuscripts must include a title page which details the following information: (1) a brief title; (2) the name of the author or authors with the highest academic degree (ie, MD, PhD); (3) a concise biographical description for each author which includes specialty, practice location, academic appointments, and primary hospital affiliation; (4) mailing address of principal author; and (5) office telephone number of principal author.

Illustrations: Authors are urged to use the services of professional illustrators and photographers. Drawings and charts should always be done in black ink on white paper. Clear, black and white glossy photographs should be submitted, and such illustrations numbered consecutively and their positions indicated in text. Original magnifications should be noted. Illustrations defaced by handwriting or excessive handling will not be accepted. The figure number, indication of the top, and the name of the author must be attached to the back of each illustration. Legends for illustrations should be type-written in a single list, with the numbers corresponding to those on photographs and drawings. Recognizable photographs of patients are to be masked and must carry with them written permission for publication.

Special arrangements must be made with the editors for excessive illustrations. Color plates are not acceptable.

Reprints: Because of cost considerations, reprints are not provided routinely to the author(s). Reprints may be ordered separately (100 copies minimum order) and printing costs will be charged to the author(s).

Responsibility: Manuscripts are subject to editorial revisions as deemed necessary by the editors and such modifications as to bring them into conformity with *Journal* style. However, neither the editors, nor the publishers, nor the Rhode Island Medical Society will accept responsibility for statements made or opinions expressed by any contributor in any article or feature published in the pages of the *Journal*.

Permission: When material is reproduced from other sources, full credit must be given to both the author and publisher of these sources. Where work is reported from a governmental service or institution, clearance by the appropriate authority must accompany the manuscript.

References: References should be limited to those citations noted in the text. The references must be typed double-spaced and numbered as they appear consecutively in the text, with their positions clearly indicated in the text. All references must be checked to assure complete accuracy. Each journal reference must include the full name of the author(s); complete title of paper; name of publication; volume number; issue number; first and last page of paper; and date (year, month, and day as indicated). Each book reference must include the full name of author(s), editor(s), or both, with initials; title of book; edition; publisher; location; year of publication, volume (if given); and page number. If the reference is to a chapter within a book, the author of the chapter, if different than the author of the book, and the title of the chapter (if any) must be provided.

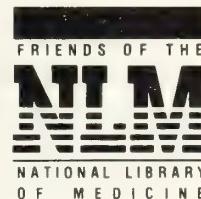
It is rarely desirable to include a complete review of the literature in the references. An alphabetized bibliography is to be used only when the listing is of books suggested for supplementary reading.

Do You Know an Impaired Physician?

Treatment of physicians for alcohol addiction shows a favorable outcome in 83 per cent of cases, and treatment of physicians for drug addiction has a 95 per cent success rate. More than 70 per cent of the physicians entering treatment return to the active practice of medicine.

The Rhode Island Medical Society Committee on Impaired Physicians, chaired by Dr Herbert Rakatansky, meets monthly. It is a standing committee of the Society charged with "helping physicians whose professional judgments and capabilities are impaired by their difficulties with chemical dependency or other illnesses."

The Committee handles inquiries in *complete confidence*. If you know of a physician who needs an advocate and support in obtaining necessary treatment, please call or write Dr Rakatansky c/o The Committee on Impaired Physicians, Rhode Island Medical Society, 106 Francis Street, Providence 02903 (401/331-3207).



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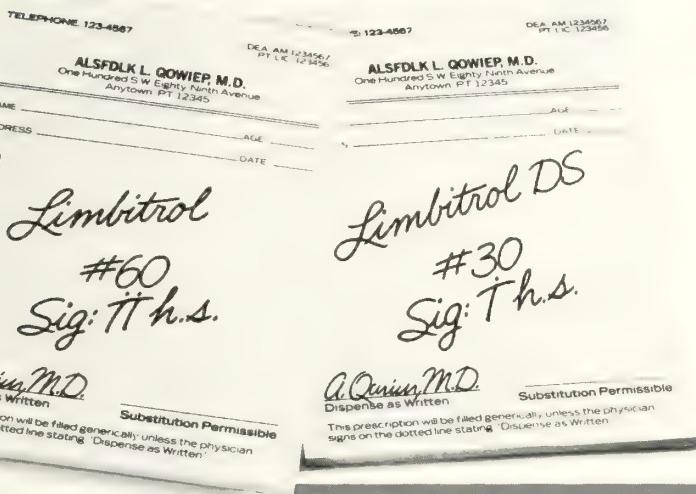
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References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Feighner VP, et al: *Psychopharmacology* 61:217-225, Mar 22, 1979.

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Before prescribing, please consult complete product information, a summary of which follows:

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants; concomitant use with MAOs or within 14 days of monoamine oxidase inhibitors (then initiate cautiously, gradually increasing dosage until optimal response is achieved); during acute recovery phase following myocardial infarction.

Warnings: Use with caution in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur when used with anticholinergics. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia, prolongation of conduction time, myocardial infarction and stroke reported with tricyclic antidepressants, especially in high doses. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs: **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. **Neurologic:** Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extra-pyramidal symptoms, syncope, changes in EEG patterns. **Anticholinergic:** Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. **Allergic:** Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus. **Hematologic:** Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. **Endocrine:** Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (anti-diuretic hormone) secretion. **Other:** Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Overdosage: Immediately hospitalize patient. Treat symptomatically and supportively. I.V. administration of 1 to 3 mg physostigmine salicylate may reverse symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

How Supplied: Double strength (DS) Tablets, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and Tablets, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.



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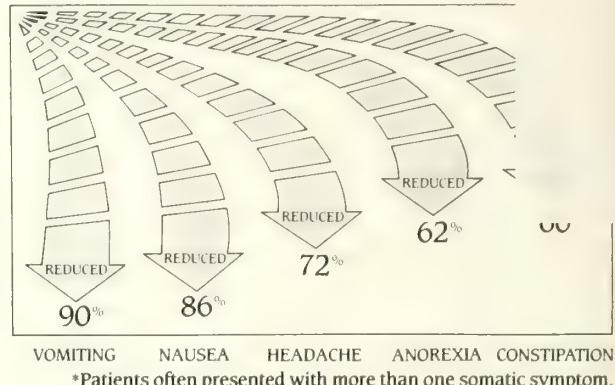
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Caution patients about the combined effects of Limbitrol with alcohol or other CNS depressants and about activities requiring complete mental alertness, such as operating machinery or driving a car. In general, limit dosage to the lowest effective amount in elderly patients.

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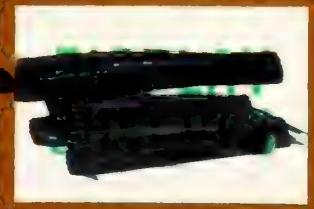
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RHODE ISLAND MEDICAL JOURNAL



October 1988

Volume 71, Number 10



The Surgeon General's Report on
NUTRITION AND HEALTH
Summary and Recommendations
(See page 391)

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 - skin/skin structure†
 - urinary tract†
 - bones and joints†
- Convenient B.I.D. dosage – 250 mg, 500 mg and 750 mg tablets

**In vitro* activity does not necessarily imply a correlation with *in vivo* results.

†Due to susceptible strains of indicated pathogens. See indicated organisms in Brief Summary.

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A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.



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BRIEF SUMMARY CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION INDICATIONS AND USAGE

Cipro[®] is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Lower Respiratory Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae*.

Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (penicillinase and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, and *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri*, and *Shigella sonnei** when antibacterial therapy is indicated.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with Cipro[®] may be initiated before results of these tests are known, once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN OR PREGNANT WOMEN. The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and very rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals. Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded. Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

Drug Interactions

Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired; concurrent administration of these agents with ciprofloxacin should be avoided.

Probencid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients

Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum concomitantly or within two hours after dosing. Ciprofloxacin may cause dizziness or lightheadedness, therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below.

Salmonella/Microsome Test (Negative)

E. coli DNA Repair Assay (Negative)

Mouse Lymphoma Cell Forward Mutation Assay (Positive)

Chinese Hamster V₇₉ Cell HGPRT Test (Negative)

Syrian Hamster Embryo Cell Transformation Assay (Negative)

Saccharomyces cerevisiae Point Mutation Assay (Negative)

Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)

Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the following three *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay

Microucleus Test (Micel)

Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in animals have not yet been completed.

Pregnancy - Pregnancy Category C

Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in

CONVENIENT B.I.D. DOSAGE

Recommended dosage schedule

Infection Site*	Severity of Infection	Dosage
Respiratory Tract*	Mild/Moderate	500 mg B.I.D.
Bone and Joint*	Severe/Complicated	750 mg B.I.D.
Urinary Tract*	Mild/Moderate	250 mg B.I.D.
	Severe/Complicated	500 mg B.I.D.
Infectious Diarrhea*	Mild/Moderate/Severe	500 mg B.I.D.

pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

Nursing Mothers

It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Ciprofloxacin should not be used in children because it causes arthropathy in immature animals (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and central nervous system (0.4%).

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below. Those typical of quinolones are italicized.

GASTROINTESTINAL (See above), painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM (See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.

SKIN/HYPERSensitivity (See above), pruritis, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivitis or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

SPECIAL SENSES blurred vision, disturbed vision, change in color perception, overbrightness of lights, decreased visual acuity, diplopia, eye pain, tinnitus, bad taste.

MUSCULOSKELETAL joint or back pain, joint stiffness, achiness, neck or chest pain, flare-up of gout.

RENAL/URINARY interstitial nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Adverse Laboratory Changes Changes in laboratory parameters listed as adverse events without regard to drug relationship.

Hepatic - Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Hematologic - eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal - Elevations of Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. In the event of serious toxic reactions from overdosage, hemodialysis or peritoneal dialysis may aid in the removal of ciprofloxacin from the body, particularly if renal function is compromised.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

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* Due to susceptible strains of indicated pathogens. See indicated organisms in Brief Summary.

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391 Surgeon General's Report on Nutrition and Health

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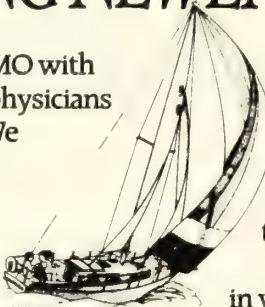
Cover: This month's JOURNAL issue contains the Summary and Recommendations of the Surgeon General's Report on Nutrition and Health from the US Department of Health and Human Services, Washington, DC. See page 391.

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EDITORIALS

The Surgeon General's Report on Nutrition and Health

On behalf of the United States Department of Health and Human Services, the Public Health Service, and the Surgeon General, I am pleased to present to the physicians of the State of Rhode Island and Providence Plantations the Summary and Recommendations of *The Surgeon General's Report on Nutrition and Health* published elsewhere in this issue of the *Journal*. This is a special privilege because your State is the first in which this Summary is being made available to all physicians.

This Report is a landmark in Public Health Service efforts to improve the health of the American people. It presents for the first time a comprehensive review of the scientific evidence that links specific dietary factors to specific chronic diseases, the policy implications of that evidence, and a set of dietary recommendations based on consensus of the Public Health Service about the significance of that evidence. Also, for the first time, this Report documents the consistency of its dietary recommendations for multiple chronic diseases, and it identifies reduction of fat intake as the primary dietary priority.

The Surgeon General's Report on Nutrition and Health was developed in response to increasing recognition that the major nutritional problems among Americans were a result of dietary excesses and imbalances rather than nutrient deficiencies. To develop the Report's recommendations, more than 50 nutrition scientists reviewed more than 2,500 scientific articles. The Report itself was reviewed by nearly 200 nutrition professionals. We believe that the results of this effort will have as great an impact as did the reports on smoking and health released by Surgeons General since 1964.

The Report calls for a national effort involving the Government in partnership with the private sector to encourage Americans to reduce the fat content of their diets. Physicians have an important role to play in this effort. I hope that you will read this Report. More than that, I hope that you and your colleagues will inform your patients about it and will incorporate its recommendations into your routine clinical advice and practice. In this way we can work together to achieve better health for the Nation.

J. Michael McGinnis, MD
Deputy Assistant Secretary for Health
(Disease Prevention and Health Promotion)
Department of Health and Human Services
Washington, DC

Definitive Treatment for the Elderly Person With Cancer

This issue of the *Journal* carries a significant article by Mor and his colleagues, which examines the degree to which the age of a cancer patient influences the physician's choice of definitive therapy. About one out of every five Rhode Island physicians had participated in and contributed to this comprehensive study.

The findings of these investigators, "... suggest that, while physicians are generally as inclined to recommend surgery at diagnosis to older patients, they are less likely to offer elders follow-up treatment (ie, radiation therapy, chemotherapy) in the year following diagnosis."

Two additional insights arise from these critical studies. First, that the science of clinical epidemiology is an increasingly powerful instrument when monitoring the quality of medical practice. And second, that the progressive aging of the population obliges us to appreciate and reevaluate the medical problems of the aged.

At the beginning of this century fewer than five per cent of Rhode Islanders were 65 years or older, and the number of these elderly who developed cancer was negligible. With an elderly population in Rhode Island at that time of about 19,700, it is likely that there were no more than 180 new cases of lung, breast, and bowel cancer per year, assuming that the age-adjusted incidence rates of 1900 are the same as the current New England rates as gathered by the National Cancer Institute.

the medical community in Rhode Island will re-examine its own pattern of recommendations for the treatment of older cancer patients in the light of the insights gained from our study."

Stanley M. Aronson, MD
Dean of Medicine Emeritus
Division of Biology and Medicine
Brown University
Providence, Rhode Island

Estimates of New Cases of Lung, Colon and Breast Cancer in Rhode Island (1900-2000)

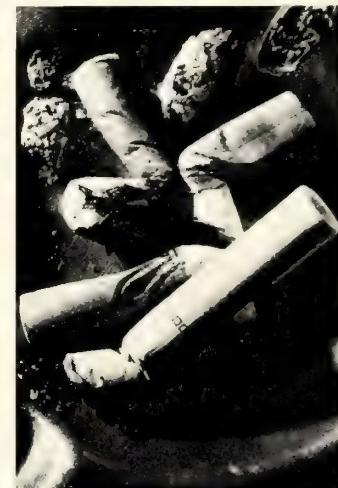
Year	Population, Total	Number & (percent)		Estimated No. New Cases of Cancer of Lung, Colon & Breast
		65-79 yrs.	80+ yrs.	
1900	428,600	16,700 (3.9%)	3,000 (0.7%)	180
1940	713,300	44,900 (6.3%)	9,300 (1.3%)	460
1980	948,000	105,200 (11.1%)	21,800 (2.3%)	1160
2000	955,000	172,000 (18.1%)	30,400 (3.2%)	1860

This space contributed as a public service.

During the succeeding nine decades as more diseases were controlled or prevented, and as our population lived longer, physicians were forced to address a paradox. Despite notable advances in health care, an increasing, rather than decreasing, percentage of our citizens were disabled. In 1900, for example, there were few frail elderly, no persons with transplanted organs, virtually no chronic diabetics, and certainly no intensive care units sustaining life in the critically ill or injured.

Furthermore, as medical and public health interventions prolong life, an increasing fraction of the population necessarily will confront diseases, such as cancer, which tend to be more frequent beyond the sixth decade of life. The accompanying table outlines the demographic changes in Rhode Island since 1900. During this century, the total state population has slightly more than doubled. The number of living Rhode Islanders older than 65 years, however, will have increased ten-fold, as will the number of new cases of cancer of the lung, bowel, and breast.

Based upon their findings, Mor and his associates conclude by expressing the hope that, " . . .



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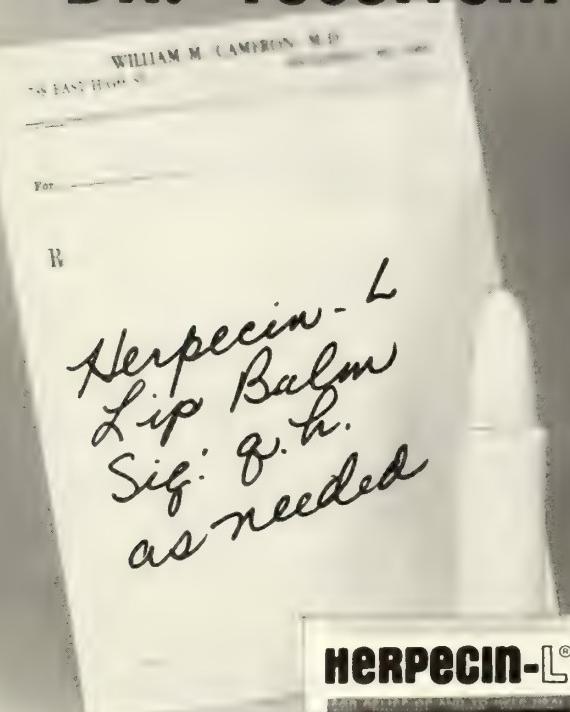
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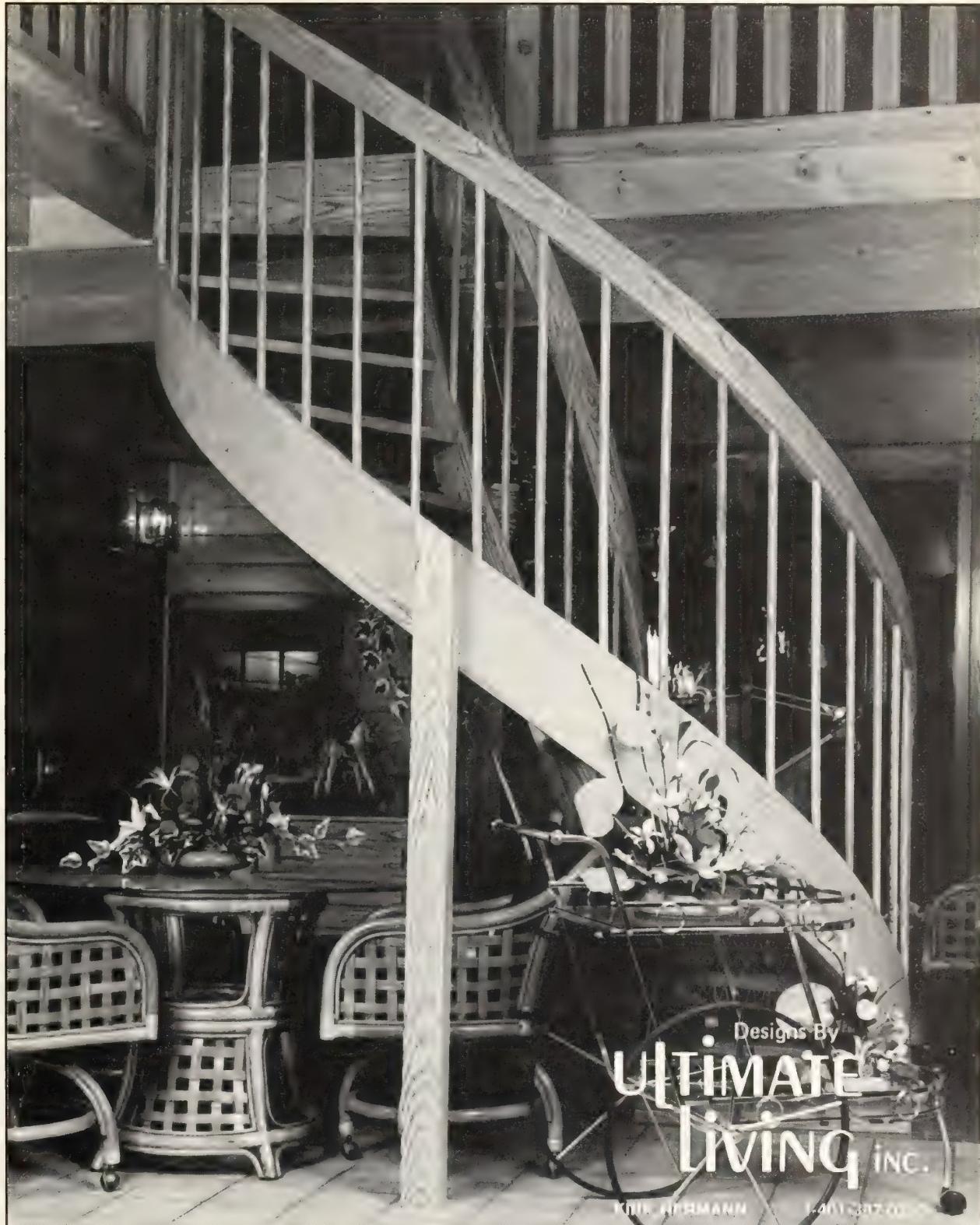
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The Brown University Cancer and Aging Study: A Statewide Cooperative Investigation

Study Provides Insights Into the Appropriate Management of Cancer in the Elderly

Vincent Mor, PhD

Edward Guadagnoli, PhD

Susan Masterson-Allen, MA

Rebecca Silliman, MD, PhD

Alan Weitberg, MD

Arvin S. Glicksman, MD

Rebecca Rosenstein, PhD

Frank J. Cummings, MD

Richard J. Goldberg, MD

Marsha D. Fretwell, MD

On March 1, 1984 the National Cancer Institute (NCI) awarded a three-year grant to the Center for Gerontology and Health Care Research (CGHCR) at Brown University to examine the influence of age on the diagnosis and management of cancer in elderly patients. The study was

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a cooperative investigation that sought to integrate the knowledge and resources of patients, physicians, and hospitals throughout Rhode Island.

The specific aims of this multi-disciplinary project were to assess the effect of patient age on (a) extent of disease at diagnosis, (b) degree of diagnostic evaluation, and (c) receipt of definitive treatment (treatment offered for cure) following diagnosis. We also sought to determine the likelihood of receiving chemotherapy or radiation therapy following initial surgical or diagnostic procedures, as well as the probability of receiving the entire treatment regimen prescribed. To achieve these aims, we documented characteristics of treatments received during the first year following diagnosis for patients with primary lung, breast, and colorectal cancer. This report provides a summary of the project's major findings.

Background

American society, like most others in the Western world, is experiencing a shift in the age distribution of its population. The proportion of people over age 65 increased from four per cent in 1900 to about 11 per cent at the present time. It has been predicted that by the year 2030 18 per cent of Americans will be over age 65.¹

The incidence rate of cancer climbs rapidly with age. Cancer incidence doubles from 497 per

100,000 between the ages of 50 through 54 to 1,032 per 100,000 between the ages of 60 through 64, and peaks in the 85+ age group with a rate of 2,308 per 100,000 population.² The death rate due to cancer also increases with age. The increase is dramatic, from 48 deaths per 100,000 between the ages of 35 and 44 to 1,434 deaths per 100,000 among persons 85 years of age or older.³

Given the predicted increase in the proportion of elderly persons in the population and the greater risk of the elderly for developing cancer, we can expect an increase in the number of elderly diagnosed as having cancer during the coming years. Past reports have repeatedly suggested that elderly patients with potentially operable cancers are more likely to present with advanced disease than are younger patients.⁴⁻⁷ Furthermore, several reports have suggested that elderly cancer patients are less likely to receive appropriate care following diagnosis than are younger patients.⁸⁻¹¹ Whether these outcomes are the result of attitudes and behavior of physicians or patients, or both, is not clear. A close examination of the influence of age, sociodemographic and medical factors, and the attitudes and preconceptions of patients, family members, and

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Marsha D. Fretwell, MD, is Head, Program in Geriatric Medicine at Roger Williams General Hospital and Associate Professor at Brown University, Providence, RI.

physicians on the diagnosis and management of cancer is needed if the elderly are to benefit equitably from advances in cancer treatment and control. The current study addresses these concerns in a newly diagnosed cohort of middle-aged and elderly cancer patients.

Methods

We identified newly diagnosed lung, breast, and colorectal cancer patients between the ages of 45 and 90 at nine Rhode Island hospitals during the period from July 1984 to February 1986. Patients eligible for study were Rhode Island residents with a histologically confirmed diagnosis. Following patient identification at hospital pathology offices, medical record abstracters confirmed study eligibility by examining hospital medical charts. Patients with a previous cancer history, *in situ* disease, or a diagnosis made at autopsy were excluded from study.

This work was funded in part by Grant CA 36560 from the National Cancer Institute. Requests for reprints should be sent to Vincent Mor, PhD, Center for Gerontology and Health Care Research, Brown University, Box G, Providence, RI 02912.

A total of 1,569 patients were identified, of whom 399 (25.4 per cent) were diagnosed as having lung cancer, 498 (31.7 per cent) with breast cancer, and 672 (42.8 per cent) colorectal cancer. Based upon statewide tumor registry estimates, patients identified in the study represent 75 per cent to 80 per cent of all lung, breast, and colorectal cancer patients diagnosed in the state during the study period. Table 1 provides a description of the characteristics of the sample by cancer type.

Medical Record Data Collection. Medical record abstracters documented initial diagnostic and treatment information for every patient who had a hospital medical record. We were able to obtain only a pathology report for a few patients (one per cent) and thus have limited information on these patients. Abstracters documented all patients treated with surgery, radiation, and chemotherapy in the year following diagnosis. In addition to hospital data collection, data were abstracted in all radiation therapy offices and in all but a few of the medical oncology practices in the state. Based on notations in surgical and other medical records examined, cancer-related medical care obtained out of state appears to be minimal. A listing of the specific data items abstracted from medical records is presented in Table 2.

**Table 1. Sample Characteristics by Cancer Type:
Brown University Cancer and Aging Study**

	Lung N = 399	Breast N = 498	Colorectal N = 672
Age			
45-64	45.9%	44.6%	28.8%
65-74	36.3	28.7	34.9
75-90	17.8	26.7	36.3
Sex			
Female	32.2	99.2	48.4
Marital Status			
Married	69.1	48.1	58.3
Employed at Diagnosis			
Yes	31.6	27.1	19.9
SES			
Poverty	10.1	14.3	11.8
Low	20.5	22.6	24.6
Middle	41.7	39.0	42.4
High	27.7	24.1	21.2
Extent of Disease			
Local	23.1	56.8	36.9
Regional	38.1	34.1	46.6
Metastatic	38.8	9.0	16.6
Other Chronic Disease			
Yes	45.2	32.2	47.2

Throughout the study, cooperation from both hospitals and physicians across the state was excellent. A total of 480 physicians participated in various phases of the project, representing approximately 20 per cent of all of the state's physicians.

Physician Treatment Recommendations. In order to obtain information related to physicians' treatment decisions, we asked surgeons involved in the initial phase of patient treatment to complete a one-page form summarizing their recommendations for post-surgical treatment and to note, from a list of pre-coded options, those factors influencing their decisions *not* to recommend particular treatments. In addition, physicians rated patients' functional performance status at the time of diagnosis using the Eastern Cooperative Oncology Group (ECOG) scale.¹² Physicians returned 1130 (73.2 per cent) of the 1542 forms mailed.

Definitions of Variables

Extent of Disease at Diagnosis. We examined the relationship between age and extent of disease for each cancer type. We used four age categories for this analysis (45-54, 55-64, 65-74, and 75-90). Extent of disease was categorized as either local (tumor contained within the anatomic boundaries of the organ of origin), regional (spread of tumor to either tissues immediately adjacent to, or lymph nodes that primarily drain, the organ of origin), or distant (spread to sites distant from the organ of origin). Male breast cancer patients were excluded from analysis.

Diagnostic Procedures and Post-Diagnostic Treatment. We sought to determine whether older patients were more or less likely to receive appropriate diagnostic procedures and definitive treatment than were younger patients. For most cancers, defining an appropriate treatment strategy following diagnosis is difficult. Many variables (eg, histologic type, location of tumor, and stage of disease) must be considered. For our analysis, we modified the definitions of Samet et al⁸ for definitive treatment (see Table 3). These include curative therapies deemed appropriate for patients with local and regional disease. Since surgery is not considered to be the treatment of choice for lung cancer patients with small-cell disease, such patients were excluded from this analysis.

Although there is a lack of consensus concerning the efficacy of chemotherapy or radiation treatment following initial surgical treatment (except for breast cancer), we also examined receipt of treatment in those instances where a high prevalence of chemotherapy or radiation indicates typical community practice. Since the vast majority of colorectal cancer patients received definitive treatment (surgery) at diagnosis, chemotherapy or radiation within the one year period following diagnosis was considered follow-up treatment. However, our observations concerning chemotherapy or radiation for lung cancer patients are not dependent upon whether pa-

Table 2. Specific Data Items Abstracted from Medical Records

Medical Data at Time of Diagnosis	Surgical Data	Radiation and/or Chemotherapy Data
Date of diagnosis	Date(s) of surgery	Treatment setting
Histologic diagnosis	Length of stay	Type of treatment
Extent of disease	Cancer spread at time of treatment	Length of treatment
Degree of disease spread	Type of surgical procedure	Cancer spread at time of treatment
Diagnostic tests performed	Post-surgical complications	Toxicity characteristics
Non-cancer diagnoses		Treatment interruption and/or termination

Table 3. Criteria Specifying Definitive Treatment*

Breast	Lung	Colorectal
Local Disease: Mastectomy, or lumpectomy followed by radiation within 5 months of diagnosis.	Local and Regional Disease: Thoracotomy plus lobectomy, or pneumonectomy.	Local and Regional Disease: Colectomy with reanastomosis, colostomy or abdominal resection. Colonoscopy with polypectomy for local disease.
Regional Disease: Mastectomy followed by adjuvant chemotherapy or hormonal therapy beginning within 5 months of diagnosis.		

* Adapted from Samet et al (1986)

tients received definitive treatment. In these instances, we simply note whether patients were treated in the year following diagnosis. Similarly, the proportion of patients with metastatic disease who received chemotherapy and radiation is stated.

While the influence of age on patient management is the primary focus of our analyses, we also assessed the influence of marital status (married vs unmarried), the presence of other diseases (cardiac or respiratory disease, or diabetes mellitus), and socio-economic status (SES) at the time of treatment. We used an SES indicator created by the Rhode Island Department of Health based on the characteristics (eg, housing, income, education) of the state's 213 census tract locations in 1980. Each patient was assigned the SES designation of the census tract of his or her residence.

Stage-specific results are presented for each cancer type. In order to shed light on factors taken into consideration in the decision *not* to recommend specific treatments, we also integrated data from Physician Treatment Recommendation Forms with these results.

Results

Extent of Disease at Diagnosis. Figure 1 displays the relationship between age and extent of disease for each cancer site. Patient age was not related to extent of disease (lung, $\chi^2(6) = 5.65$, $p > .05$; breast $\chi^2(6) = 7.31$, $p > .05$; colorectal, $\chi^2(6) = 5.06$, $p > .05$). Similarly, for each cancer type, chi-square tests for trend ($df = 1$) did not reveal an age relationship at any level of disease.¹³

Since a previous investigation examined male lung cancer patients only,¹⁴ we analyzed our data separately for male and female lung cancer patients. Among male lung cancer patients ($N = 270$) we observed a statistically significant inverse relationship ($\chi^2(6) = 12.85$, $p < .05$) between age and extent of disease. The percentage of males

diagnosed as having local disease increased from 21 per cent for 45-54 year olds to 35 per cent for patients over the age of 74. This relationship was not observed among female ($N = 129$) patients ($\chi^2(6) = 8.22$, $p > .05$).

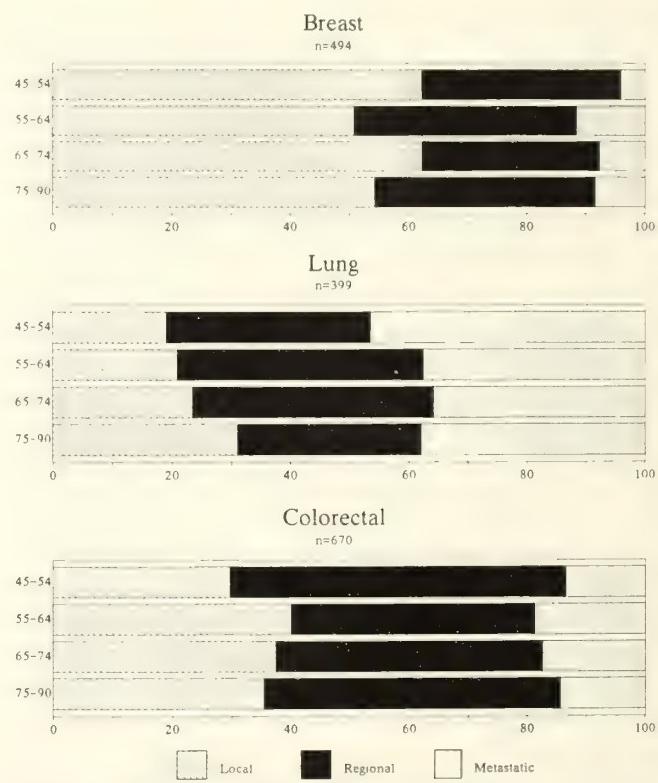


Fig 1. Percentage of cases with local, regional, or metastatic disease by age at diagnosis and cancer type.

Diagnostic Procedures and Post-Diagnostic Treatment

Breast Cancer. Patients in the oldest age group (75 and older) were less likely to receive appropriate diagnostic evaluation (mammography and biopsy) than were patients in the youngest age group (72 per cent vs 59 per cent; $p < .02$). This

pattern held when mammography and breast biopsy were examined separately, although for mammography the age effect was confined to women with local disease (66.2 per cent vs. 92.5 per cent; $p < .0001$).¹⁵

The majority (70 per cent; $N = 194$) of patients with local disease had some form of mastectomy, and nearly one-third (30 per cent; $N = 84$) received lumpectomy. Of those who received lumpectomy, over one-third (39 per cent; $N = 33$) did not receive subsequent radiation therapy. Our analysis revealed that women over the age of 74 were only one-fifth as likely to receive radiation therapy as were women under age 65 (Odds Ratio (OR) = .212; 95 per cent Confidence Limits = .053, .857). Neither marital status, co-morbidity status, nor SES was related to receipt of radiation following lumpectomy.¹⁵ Physicians returned Treatment Recommendation Forms for 57 of the 84 local disease patients who had a lumpectomy. These data revealed that physicians recommended follow-up radiation for 37 (65 per cent) patients, only four of whom did not actually receive radiation. The most common reason offered for not recommending radiation was that it was inappropriate for patient's stage of disease (eight cases). Patient and family factors accounted for another six cases, only one of which cited the patient's age as a prohibiting factor.

The vast majority (91 per cent; $N = 154$) of patients diagnosed as having regional breast cancer received some form of mastectomy. However, nearly half of these patients did not receive adjuvant chemotherapy (47 per cent; $N = 73$). Once again, of all patient characteristics examined, only age was related to whether or not chemotherapy or hormonal therapy was administered. Older women received the treatment less often than younger women. Of the 38 Treatment Recommendation Forms returned by physicians who did not recommend adjuvant chemotherapy or hormonal therapy, the majority (82 per cent; $N = 31$) indicated that treatment was not applicable for the patient's stage of disease. In only three instances did physicians attribute patient factors as important reasons for not recommending treatment.

We also examined treatment patterns over the first year after diagnosis for metastatic breast cancer patients. Two thirds (66 per cent; $N = 29$) of the patients received chemotherapy, and nearly two-fifths (39 per cent; $N = 17$) were given radiation therapy. In this group of patients with advanced disease, age was not related to whether or not either type of treatment was given.

Lung Cancer. We determined whether patients received procedures to assess spread of disease to four areas generally associated with dissemination of lung cancer (chest, brain, liver and bone). In general, age was not related to whether procedures were employed to assess tumor spread to these areas. The only significant age effect was noted for regional disease patients. Patients in the oldest age group (75-90) were less likely to undergo brain Computed Tomography (CT) than were younger patients (13.6 per cent vs 31 per cent of those under 65 and 50.8 per cent of those aged 65-74; $p < .01$). For most procedures, as expected, the prevalence of a particular test increased with the presence of more extensive disease.

Most (67 per cent; $N = 62$) patients with local disease and nearly half (48 per cent; $N = 73$) with regional disease received definitive treatment following diagnosis (see Table 3 for our definition of definitive treatment). However, local disease patients over age 74 received definitive treatment less often than did younger patients (44 per cent aged 75-90 vs 66 per cent aged 65-74 and 81 per cent under age 65; $p < .05$). Receipt of definitive treatment did not vary as a function of age among regional disease patients. Neither sex, marital status, chronic disease status, nor SES was related to whether or not local or regional disease patients were treated definitively.¹⁶

In addition to definitive treatment following diagnosis, we also examined the use of chemotherapy and radiation treatment within the year following diagnosis. Overall, 20 per cent ($N = 18$) of local, 37 per cent ($N = 56$) of regional, and 39 per cent ($N = 60$) of patients with metastatic lung disease received some form of chemotherapy in the first year after diagnosis. Among non-local disease patients, older patients were less likely to receive chemotherapy than were younger patients. Regional disease patients aged 75-90 were less likely to receive chemotherapy following diagnosis than were patients under age 75 (nine per cent aged 75-90 vs 42 per cent of those aged 65-74 and 41 per cent of those under age 65; $p < .05$). Among metastatic disease patients, those 65-74 years old (33 per cent) and patients older than 75 years (22 per cent) were less likely to receive chemotherapy than were those under 65 (50 per cent; $p < .05$).

Radiation therapy was given more often to advanced lung cancer patients. A greater proportion of regional (63 per cent; $N = 96$) and metastatic (56 per cent; $N = 86$) disease patients

received radiation than did patients with local (26 per cent; N = 18) disease. Neither age, sex, co-morbidity, SES, nor marital status was related to whether or not treatment was received for either local or metastatic disease. However, among regional disease patients, multivariate analysis revealed that 75-90 year old patients were less likely than patients under 65 to receive radiation treatment.

Colorectal Cancer. We found that regardless of extent of disease older patients were as likely as younger patients to receive a procedure to assess spread of disease outside the colon or rectum. Seventeen per cent of local disease patients, 32 per cent of regional disease patients, and 45 per cent of metastatic disease patients received at least one abdominal diagnostic procedure (eg, liver scan or CT scan of the abdomen or pelvis).

Few colorectal cancer patients did *not* receive definitive treatment (local: N = 19, eight per cent; regional: N = 10, three per cent). Whether or not treatment was received was not related to patient age regardless of extent of disease; nor was it related to any other of the patient factors examined (marital status, co-morbidity, SES).

Although the prevalence of chemotherapy was low for patients with local (one per cent) or regional disease (eight per cent), slightly more than a quarter (26 per cent; N = 29) of the metastatic disease patients received this form of treatment. Among this group of patients, the likelihood of being treated declined markedly with age, with six per cent of patients over age 74 receiving treatment, compared to 34 per cent of patients aged 65-74 and 38 per cent of patients under age 65 ($p < .05$).

Only six per cent (N = 15) of local disease patients received radiation treatment within 12 months of diagnosis. An identical percentage (14 per cent) of regional (N = 44) and metastatic disease patients (N = 16) received treatment. For regional disease patients, the likelihood of receipt of radiation therapy declined with age. Thirteen per cent (13 per cent) of patients aged 65-74 and five per cent of patients over age 74 received radiation therapy, compared to 28 per cent of patients under age 65 ($p < .05$). The small number of patients with metastatic disease treated with radiation prevented the detection of age difference, if any existed.

Discussion

We examined the influence of age and other patient factors on extent of disease at diagnosis, receipt of diagnostic procedures, and cancer

treatment patterns in a sample of breast, lung, and colorectal cancer patients newly diagnosed at nine Rhode Island hospitals between July 1984 and February 1986. Patient age was not related to extent of disease at diagnosis, with the exception that older male lung cancer patients were diagnosed when disease was less extensive than were younger patients. However, age was the single most important determinant of the less frequent receipt of both mammography and biopsy by older women (75+) with breast cancer. Similarly, older breast cancer patients and older lung cancer patients with local disease were less likely than younger patients to receive definitive treatment at the time of diagnosis. Finally, when examined by stage of disease, age appeared to influence whether some lung and colorectal cancer patients received chemotherapy and radiation.

Our findings regarding stage of disease at diagnosis among breast cancer patients are contrary to past studies in which older patients were found to be more likely than younger to be diagnosed as having advanced disease.⁴⁻⁷ However, the patients in our sample were diagnosed between 1984-1986, while past research largely involved patients diagnosed before 1980. It may be that societal factors, particularly an increasing nationwide emphasis on health promotion, have positively influenced the attitudes and behaviors of both patients and physicians, resulting in earlier recognition of symptoms and more regular screening practices. The lack of an age difference in extent of disease at diagnosis for colorectal cancer patients is in agreement with previous research,^{4, 5, 7} as is the inverse age effect observed in our study for male lung cancer patients.⁷

While the elderly do not appear to be at a disadvantage at the time of disease presentation in comparison to their middle-aged counterparts, the picture regarding disease management following presentation is less encouraging. Age differences in extent of diagnostic work-up for breast cancer patients support the findings of Chu and his colleagues.¹¹ They investigated the influence of age on diagnostic test performance within the Community Hospital Oncology Program and found that breast cancer patients over the age of 75 with local disease were less likely to have had lymph node dissections than were patients between 45 and 74 (72 per cent vs 91 per cent). Among patients with regional breast cancer, older women had fewer lymph nodes examined than did younger women. Similar age differences were reported for mammography. Stage misclassification (ie, classifying breast can-

cer at a less advanced stage than is actually the case) and the resulting undertreatment is a potential hazard for those breast cancer patients who do not receive an adequate diagnostic work-up.

Other recent investigations of the influence of age on cancer treatment patterns support the findings of our study.⁸⁻¹¹ Samet et al,⁸ employing New Mexico tumor registry data, reported that older patients with a variety of cancer types were less likely to receive definitive treatment (treatment offered for cure). Greenfield et al¹⁰ found that breast cancer patients with the greatest potential for cure, those with local disease and no accompanying chronic illness, were treated differently as a function of age. Fewer older patients received appropriate care. Finally, recent evidence suggests that, given the same disease, older patients receive radiation and chemotherapy treatment less often than do younger patients.^{9,11}

While post-surgical radiation is now universally recommended for persons with local disease who have breast-conserving surgery, only 60 per cent of the patients in our study received such treatment. Similarly, only 50 per cent of regional disease breast cancer patients received adjuvant chemotherapy or hormonal therapy following surgery. Since there is now solid evidence for the life-prolonging benefit of adjuvant treatment,¹⁷ these findings suggest an inadequacy in the dissemination of this information in the medical community.

It is striking that age was the *only* predictor of definitive treatment receipt for breast cancer patients. Furthermore, the suggestion of age as a factor is reinforced in our findings regarding the less frequent receipt of chemotherapy and radiation by older lung and colorectal cancer patients as compared to younger patients. Samet et al⁸ speculated that their findings concerning the influence of age on receipt of cancer treatment may actually have been a reflection of the influence of co-morbidity or poor performance status. However, our determination of co-morbidity was *not* related to differential treatment patterns for any cancer site or stage of disease examined. Furthermore, physicians' functional status ratings of breast cancer patients at diagnosis revealed that over 90 per cent had no functional impairment.

Examination of the reasons physicians gave for not recommending treatment did not reveal any underlying rationale for the differential patterns of treatment by age. Only rarely did a physician cite age as a factor in his or her consideration. Patient and family disinclination to accept treat-

ment accounted for only a small proportion of cases. The most frequently offered reasons — inappropriate treatment for the stage of patient's disease and lack of proven efficacy of treatment — are puzzling in the case of breast cancer, for which there is a consensus regarding definitive treatment.¹⁷ Treatment-related reasons are more understandable with regard to lung and colorectal cancer, where evidence of long-term efficacy is lacking.

In addition to illuminating the reasoning underlying disease management, our treatment recommendation data also clearly indicate the primary importance of physician recommendations on actual treatment. Only a small minority of patients who were advised to receive specific treatments did not receive them, suggesting that patients and families are usually compliant with recommendations for treatment.

The findings further suggest that, physicians are generally as disposed to recommend surgery to older patients as they are to younger patients. They are however less likely to offer older patients follow-up treatment in the year following diagnosis. The data suggest that physicians are more likely to attribute the unpleasant consequences of chemotherapy and radiation treatment to advanced years in the case of the elderly. However, studies assessing the side effects of chemotherapy^{18,19} and radiation treatment²⁰ indicate only minimal age-related differences in treatment-related toxicity.

Appropriate management of the elderly individual with cancer requires an in-depth understanding of the complex factors involved in decision-making by patients, families, and physicians. Dispelling the misconception that advanced age is inextricably linked with low tolerance to treatment, even in the absence of co-morbid conditions or physical debilitation, may result in an increased five year survival for the "old old" segment of the cancer patient population. The Cancer and Aging Study has taken us one step further in providing information that will enhance our collective understanding of these complex issues. We hope that the medical community in Rhode Island will re-examine its own pattern of recommendations for the treatment of older cancer patients in light of the insights gained from our study.

Acknowledgments

The impressive volume of data collected for the Cancer and Aging Study would not have been possible without the cooperation of many phy-

sicians, their staffs, and, most of all, their patients. Study investigators at Brown University extend sincere thanks to project staff and to all who have made this study a true model of collaborative research.

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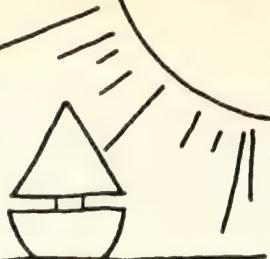
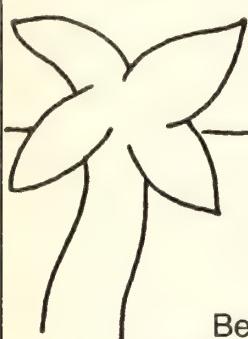
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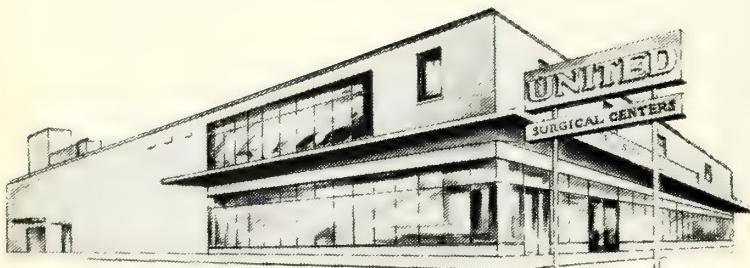


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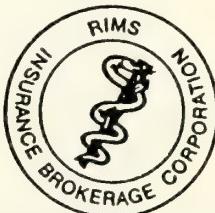
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Surgeon General's Report on Nutrition and Health

Summary and Recommendations

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Hippocrates (460-377 B.C.)

This Report addresses the substantial impact of daily dietary patterns on the health of Americans. Good health does not always come easily. It is the product of complex interactions among environmental, behavioral, social, and genetic factors. Some of these are, for practical purposes, beyond personal control. But there are many ways in which each of us can influence our chances for good health through the daily choices we make.

In recent years, scientific investigations have produced abundant information on the ways personal behavior affects health. This information can help us decide whether to smoke, when and how much to drink, how far to walk or climb stairs, whether to wear seat belts, and how or whether to engage in any other activity that might alter the risk of incurring disease or disability. For the two out of three adult Americans who do not smoke and do not drink excessively, one personal choice seems to influence long-term health prospects more than any other: what we eat.

Food sustains us, it can be a source of considerable pleasure, it is a reflection of our rich social fabric and cultural heritage, it adds valued dimensions to our lives. Yet what we eat may affect our risk for several of the leading causes of death

for Americans, notably, coronary heart disease, stroke, atherosclerosis, diabetes, and some types of cancer. These disorders together now account for more than two-thirds of all deaths in the United States.

Undernutrition remains a problem in several parts of the world, as well as for certain Americans. But for most of us the more likely problem has become one of overeating — too many calories for our activity levels and an imbalance in the nutrients consumed along with them. Although much is still uncertain about how dietary patterns protect or injure human health, enough has been learned about the overall health impact of the dietary patterns now prevalent in our society to recommend significant changes in those patterns.

This first *Surgeon General's Report on Nutrition and Health* offers comprehensive documentation of the scientific basis for the recommended dietary changes. Through the extensive review contained in its chapters, the Report examines in detail current knowledge about the relationships among specific dietary practices and specific disease conditions and summarizes the implications of this information for individual food choices, public health policy initiatives, and further research. The Report's main conclusion is that overconsumption of certain dietary components is now a major concern for Americans. While many food factors are involved, chief among them is the disproportionate consumption of foods high in fats, often at the expense of foods high in complex carbohydrates and fiber that may be more conducive to health. A list of the key recommendations based on the evidence presented in the Report is provided in Table 1.

Table 1. Recommendations

Issues for Most People:

- **Fats and cholesterol:** Reduce consumption of fat (especially saturated fat) and cholesterol. Choose foods relatively low in these substances, such as vegetables, fruits, whole grain foods, fish, poultry, lean meats, and low-fat dairy products. Use food preparation methods that add little or no fat.
- **Energy and weight control:** Achieve and maintain a desirable body weight. To do so, choose a dietary pattern in which energy (caloric) intake is consistent with energy expenditure. To reduce energy intake, limit consumption of foods relatively high in calories, fats, and sugars, and minimize alcohol consumption. Increase energy expenditure through regular and sustained physical activity.
- **Complex carbohydrates and fiber:** Increase consumption of whole grain foods and cereal products, vegetables (including dried beans and peas), and fruits.
- **Sodium:** Reduce intake of sodium by choosing foods relatively low in sodium and limiting the amount of salt added in food preparation and at the table.
- **Alcohol:** To reduce the risk for chronic disease, take alcohol only in moderation (no more than two drinks a day), if at all. Avoid drinking any alcohol before or while driving, operating machinery, taking medications, or engaging in any other activity requiring judgment. Avoid drinking alcohol while pregnant.

Other Issues for Some People:

- **Fluoride:** Community water systems should contain fluoride at optimal levels for prevention of tooth decay. If such water is not available, use other appropriate sources of fluoride.
- **Sugars:** Those who are particularly vulnerable to dental caries (cavities), especially children, should limit their consumption and frequency of use of foods high in sugars.
- **Calcium:** Adolescent girls and adult women should increase consumption of foods high in calcium, including low-fat dairy products.
- **Iron:** Children, adolescents, and women of childbearing age should be sure to consume foods that are good sources of iron, such as lean red meats, fish, certain beans, and iron-enriched cereals and whole grain products. This issue is of special concern for low-income families.

Magnitude of the Problem

Diet has always had a vital influence on health. Until as recently as the 1940s, diseases such as rickets, pellagra, scurvy, beriberi, xerophthalmia, and goiter (caused by lack of adequate dietary vitamin D, niacin, vitamin C, thiamin, vitamin A, and iodine, respectively) were prevalent in this country and throughout the world. Today, thanks to an abundant food supply, fortification of some foods with critical trace nutrients, and better methods for determining and improving the nutrient content of foods, such "deficiency" diseases have been virtually eliminated in devel-

oped countries. For example, the introduction of iodized salt in the 1920s contributed greatly to eliminating iodine-deficiency goiter as a public health problem in the United States. Similarly, pellagra disappeared subsequent to the discovery of the dietary causes of this disease. Nutrient deficiencies are reported rarely in the United States, and the few cases of protein-energy malnutrition that are listed annually as causes of death generally occur as a secondary result of severe illness or injury, child neglect, the problems of the house-bound aged, premature birth, alcoholism, or some combination of these factors.

As the diseases of nutritional deficiency have diminished, they have been replaced by diseases of dietary excess and imbalance — problems that now rank among the leading causes of illness and death in the United States, touch the lives of most Americans, and generate substantial health care costs. Table 2, for example, lists the ten leading causes of death in the United States in 1987.

In addition to the five of these causes that scientific studies have associated with diet (coronary heart disease, some types of cancer, stroke, diabetes mellitus, and atherosclerosis), another three — cirrhosis of the liver, accidents, and suicides — have been associated with excessive alcohol intake. Together, these eight conditions ac-

Table 2. Estimated Total Deaths and Per Cent of Total Deaths for the 10 Leading Causes of Death: United States, 1987

Rank	Cause of Death	Number	Per Cent of Total Deaths
1 ^a	Heart diseases (Coronary heart disease) (Other heart disease)	759,400 (511,700) (247,700)	35.7 (24.1) (11.6)
2 ^a	Cancers	476,700	22.4
3 ^a	Strokes	148,700	7.0
4 ^b	Unintentional injuries (Motor vehicle) (All others)	92,500 (46,800) (45,700)	4.4 (2.2) (2.2)
5	Chronic obstructive lung diseases	78,000	3.7
6	Pneumonia and influenza	68,600	3.2
7 ^a	Diabetes mellitus	37,800	1.8
8 ^b	Suicide	29,600	1.4
9 ^b	Chronic liver disease and cirrhosis	26,000	1.2
10 ^a	Atherosclerosis	23,100	1.1
	All causes	2,125,100	100.0

^a Causes of death in which diet plays a part.

^b Causes of death in which excessive alcohol consumption plays a part.

Source: National Center for Health Statistics, *Monthly Vital Statistics Report*, vol. 37, no. 1, April 25, 1988.

counted for nearly 1.5 million of the 2.1 million total deaths in 1987, and they continue to inflict a substantial burden of illness on Americans. For example:

- **Coronary Heart Disease.** Despite the recent sharp decline in the death rate from this condition, coronary heart disease still accounts for the largest number of deaths in the United States. More than 1.25 million heart attacks occur each year (two-thirds of them in men), and more than 500,000 people die as a result. In 1985, illness and deaths from coronary heart disease cost Americans an estimated \$49 billion in direct health care expenditures and lost productivity.
- **Stroke.** Strokes occur in about 500,000 persons per year in the United States, resulting in nearly 150,000 deaths in 1987 and long-term disability for many individuals. Approximately two million living Americans suffer from stroke-related disabilities, at an estimated annual cost of more than \$11 billion.
- **High Blood Pressure.** High blood pressure (hypertension) is a major risk factor for both heart disease and stroke. Almost 58 million people in the United States have hypertension, including 39 million who are under age 65. The occurrence of hypertension increases with age and is higher for black Americans (of which 38 per cent are hypertensive) than for white Americans (29 per cent).
- **Cancer.** More than 475,000 persons died of cancer in the United States in 1987, making it the second leading cause of death in this country. During the same period, more than 900,000 new cases of cancer occurred. The costs of cancer for 1985 have been estimated to be \$22 billion for direct health, \$9 billion in lost productivity due to treatment or disability, and \$41 billion in lost productivity due to premature mortality, for a total cost of \$72 billion.
- **Diabetes Mellitus.** Approximately 11 million Americans have diabetes, but almost half of them have not been diagnosed. In addition to the nearly 38,000 deaths in 1987 attributed directly to this condition, diabetes also contributes to an estimated 95,000 deaths per year from associated cardiovascular and kidney complications. In 1985, diabetes was estimated to cost \$13.8 billion per year, or about 3.6 per cent of total health care expenses.
- **Obesity.** Obesity affects approximately 34 million adults ages 20 to 74 years in the United States, with the highest rate observed among

the poor and minority groups. Obesity is a risk factor for coronary heart disease, high blood pressure, diabetes, and possibly some types of cancer as well as other chronic diseases.

- **Osteoporosis.** Approximately 15 to 20 million Americans are affected by osteoporosis, which contributes to some 1.3 million bone fractures per year in persons 45 years and older. One-third of women 65 years and older have vertebral fractures. On the basis of x-ray evidence, by age 90 one-third of women and one-sixth of men will have suffered hip fractures, leading to death in 12 to 20 per cent of those cases and to long-term nursing care for many who survive. The total costs of osteoporosis to the US economy were estimated to be \$7 to \$10 billion in 1983.
- **Dental Diseases.** Dental caries and periodontal disease continue to affect a large proportion of Americans and cause substantial pain, restriction of activity, and work loss. Although dental caries among children, as well as some forms of adult periodontal disease, appear to be declining, the overall prevalence of these conditions imposes a substantial burden on Americans. The costs of dental care were estimated at \$21.3 billion in 1985.
- **Diverticular Disease.** Because most persons with diverticular disease do not have symptoms, the true prevalence of this condition is unknown. Frequency increases with age, and up to 70 per cent of people between the ages of 40 and 70 may be affected. In 1980, diverticulosis was accountable for some 200,000 hospitalizations.

In assessing the role that diet might play in prevention of these conditions, it must be understood that they are caused by a combination (and interaction) of multiple environment, behavioral, social, and genetic factors. The exact proportion that can be attributed directly to diet is uncertain. Although some experts have suggested that dietary factors overall are responsible for perhaps a third or more of all cases of cancer, and similar estimates have been made for coronary heart disease, such suggestions are based on interpretations of research studies that cannot completely distinguish dietary from genetic, behavioral, or environmental causes.

We know, for example, that cigarette smoking exerts a powerful influence on the occurrence of both coronary heart disease and some types of cancer. We also know that some people are genetically predisposed to coronary heart disease, stroke, and diabetes and that the interaction of genetic predisposition with dietary patterns is an

important determinant of individual risk. For these reasons, it is not yet possible to determine the proportion of chronic diseases that could be reduced by dietary changes. Nonetheless, it is now clear that diet contributes in substantial ways to the development of these diseases and that modification of diet can contribute to their prevention. The magnitude of the health and economic cost of diet-related disease suggests the importance of the dietary changes suggested. This Report reviews these issues in detail.

Nature of the Evidence

Whereas centuries of clinical observations and decades of basic and clinical research prove that dietary deficiencies of single, identifiable nutrients can cause disease, research on the relationship of dietary excesses and imbalances to chronic disease yields results that rarely provide such direct proof of causality. Instead, investigators must piece together various kinds of information from several kinds of sources. Nevertheless, the quantity of current animal, laboratory, clinical, and epidemiologic evidence that associates dietary excesses and imbalances with chronic disease is substantial and, when evaluated according to established principles, compelling.

Scientists must often draw inferences about the relationships between dietary factors and disease from laboratory animal studies or human metabolic and population studies that approach the issues indirectly. Data sources for such human studies include clinical and laboratory measurements of physiologic indicators of nutritional status or risk factors, as well as dietary intake data estimated for populations or individuals. Epidemiologic studies using these data compare dietary intake and disease rates in different countries or in defined groups within the same country.

Interpretations of animal studies are limited by uncertainties about their applicability to people. Clinical, laboratory, and dietary intake studies can provide useful information, but each has limitations. Currently available clinical and laboratory measurements reveal only a small part of the complex physiological responses to diet, and they may reflect past rather than current nutritional status. Dietary surveys depend on accurate recall of the types and portion sizes of consumed foods as well as on the assumption that the food intake during any one period represents typical intake. Reported intake, however, is not always accurate, and intake reported for a given period may differ significantly from that typical

of longer time periods. Dietary intake data provide useful indicators for populations, but even when an association or correlation between a dietary factor and a disease is observed, it is often difficult to prove that the dietary factor is an actual or sole cause of that disease.

This difference between association and causation is basic to understanding the scientific evidence that links diet to chronic disease. Uncertainties in the ability to determine causation have sometimes made it difficult to achieve consensus on appropriate public health nutrition policies. Established principles require evaluation of the supporting evidence for a given association between a dietary factor and a disease on the basis of its consistency, strength, specificity, and biological plausibility. The evidence showing that dietary intake of saturated fat raises blood cholesterol, which in turn increases the chance of coronary heart disease, illustrates this point. The similarity in results from laboratory, clinical, and epidemiologic research, the apparent relationship between dose and effect in these studies, the observations that the increase in blood cholesterol level is specific to saturated fatty acids but not to other types, and the biological plausibility of explanations for the observations, when taken together, provide considerable support for concluding that the association is causal, at least for some individuals.

For some of the other diseases reviewed in this Report, the available evidence is less complete and less consistent. Nevertheless, much evidence supports credible associations between a dietary pattern of excesses and imbalances and several important chronic diseases. These associations, in turn, suggest that the overall health of Americans could be improved by a few specific but fundamental dietary changes.

Key Findings and Recommendations

Even though the results of various individual studies may be inconclusive, the preponderance of the evidence presented in the Report's comprehensive scientific review substantiates an association between dietary factors and rates of chronic diseases. In particular, the evidence suggests strongly that a dietary pattern that contains excessive intake of food high in calories, fat (especially saturated fat), cholesterol, and sodium, but that is low in complex carbohydrates and fiber, is one that contributes significantly to the high rates of major chronic diseases among Americans. It also suggests that reversing such dietary patterns should lead to a reduced inci-

dence of these chronic diseases.

This *Surgeon General's Report on Nutrition and Health* provides a comprehensive review of the most important scientific evidence in support of current Federal nutrition policy as stated in the *Dietary Guidelines for Americans*. These *Guidelines*, issued jointly by the Department of Agriculture and the Department of Health and Human Services, recommend:

- Eat a variety of foods.
- Maintain desirable weight.
- Avoid too much fat, saturated fat, and cholesterol.
- Eat foods with adequate starch and fiber.
- Avoid too much sugar.
- Avoid too much sodium.
- If you drink alcoholic beverages, do so in moderation.

Evidence presented in this Report expands the focus of these seven guidelines and provides considerable insight into priorities. Clearly emerging as the primary priority for dietary change is the recommendation to reduce intake of total fats, especially saturated fat, because of their relationship to development of several important chronic disease conditions. Because excess body weight is a risk factor for several chronic diseases, maintenance of desirable weight is also an important public health priority. Evidence further supports the recommendation to consume a dietary pattern that contains a variety of foods, provided that these foods are generally low in calories, fat, saturated fat, cholesterol, and sodium.

Taken together, the recommendations in this Report promote a dietary pattern that emphasizes consumption of vegetables, fruits, and whole grain products — foods that are rich in complex carbohydrates and fiber and relatively low in calories — and of fish, poultry prepared without skin, lean meats, and low-fat dairy products selected to minimize consumption of total fat, saturated fat, and cholesterol.

The evidence presented in this Report suggests that such overall dietary changes will lead to substantial improvements in the nutritional quality of the American diet. Consuming a higher proportion of calories from fruits, vegetables, and grains may lead to a modest reduction in protein intake for some people, but this reduction is unlikely to impair nutritional status. Average levels of protein consumption in the United States, 60 grams per day for women and 90 grams per day for men, are well above the National Research

Council's recommendations of 44 and 56 grams per day, respectively.

The evidence also suggests that most Americans generally need not consume nutrient supplements. An estimated 40 per cent of Americans consume supplemental vitamins, minerals, or other dietary components at an annual cost of more than \$1.5 billion. Although nutrient supplements are usually safe in amounts corresponding to the Recommended Dietary Allowances (and such Allowances are set to ensure that the nutrient needs of practically all the population are met), there are no known advantages to healthy people consuming excess amounts of any nutrient, and amounts greatly exceeding recommended levels can be harmful. For example, some nutrients such as selenium have a narrow range of safe level of intake. Toxicity has been reported for most minerals and trace elements, as well as some vitamins, indicating that excessive supplementation with these substances can be hazardous.

Finally, some recommendations for dietary change apply broadly to the general public whereas others apply only to specific population groups. These major findings and recommendations of the *Surgeon General's Report on Nutrition and Health* are noted below.

Issues for Most People

● Fats and cholesterol: Reduce consumption of fat (especially saturated fat) and cholesterol. Choose foods relatively low in these substances, such as vegetables, fruits, whole grain foods, fish, poultry, lean meats, and low-fat dairy products. Use food preparation methods that add little or no fat. High intake of total dietary fat is associated with increased risk for obesity, some types of cancer, and possibly gallbladder disease. Epidemiologic, clinical, and animal studies provide strong and consistent evidence for the relationship between saturated fat intake, high blood cholesterol, and increased risk for coronary heart disease. Conversely, reducing blood cholesterol levels reduces the risk for death from coronary heart disease. Excessive saturated fat consumption is the major dietary contributor to total blood cholesterol levels. Dietary cholesterol raises blood cholesterol levels in most people, but the effect is less pronounced than that of saturated fat. While polyunsaturated fatty acid consumption, and probably monounsaturated fatty acid consumption, lowers total blood cholesterol, the precise effects of specific fatty acids are not well defined.

Dietary fat contributes more than twice as many calories as equal quantities (by weight) of either protein or carbohydrate, and some studies indicate that diets high in total fat are associated with higher obesity rates. In addition, there is substantial, although not yet conclusive, epidemiologic and animal evidence in support of an association between dietary fat intake and increased risk for cancer, especially breast and colon cancer. Similarly, epidemiologic studies suggest an association between gallbladder disease, excess caloric intake, high dietary fat, and obesity. More precise conclusions about the role of dietary fat await the development of improved methods to distinguish among the contributions of the high-calorie, high-fat, and low-fiber components of current American dietary patterns.

At present, dietary fat accounts for about 37 per cent of the total energy intake of Americans — well above the upper limit of 30 per cent recommended by the American Heart Association and the American Cancer Society, and above the per cent consumed by many societies, such as Mediterranean countries, Japan, and China, for example, where coronary heart disease rates are much lower than those observed in the United States. Consumption of saturated fat and cholesterol is also substantially higher among many Americans than levels recommended by several expert groups.

The major dietary sources of fat in the American diet are meat, poultry, fish, dairy products, and fats and oils. Animal products tend to be higher in both total and saturated fats than most plant sources. Although some plant fats such as coconut and palm kernel oils also contain high proportions of saturated fatty acids, these make minor contributions to total intake of saturated fats in the United States. Dietary cholesterol is found only in foods of animal origin, such as eggs, meat, poultry, fish, and dairy products. To help reduce consumption of total fat, especially saturated fat and cholesterol, food choices should emphasize intake of fruits, vegetables, and whole grain products and cereals. They should also emphasize consumption of fish, poultry prepared without skin, lean meats, and low-fat dairy products. Among vegetable fats, those that are more unsaturated are better choices.

- *Energy and weight control:* Achieve and maintain a desirable body weight. To do so, choose a dietary pattern in which energy (caloric) intake is consistent with energy expenditure. To reduce energy intake, limit consumption of foods

relatively high in calories, fats, and sugars and minimize alcohol consumption. Increase energy expenditure through regular and sustained physical activity.

People are considered overweight if their body mass index, or BMI (a ratio of weight to height described in the Report), exceeds the 85th percentile for young American adults (approximately 120 per cent of desirable body weight); they are considered severely overweight if their BMI exceeds the 95th percentile (approximately 140 percent of desirable body weight). Overweight individuals are at increased risk for diabetes mellitus, high blood pressure and stroke, coronary heart disease, some types of cancer, and gallbladder disease. Epidemiologic and animal studies have shown consistently that overall risk for death is increased with excess weight, with risk increasing as severity of obesity increases.

Type II (noninsulin-dependent) diabetes mellitus accounts for approximately 90 per cent of all cases of diabetes and is strongly associated with obesity. Clinical studies indicate that weight loss can improve control of Type II diabetes.

Obesity increases the risk for high blood pressure, and consequently for stroke; it also increases blood cholesterol levels associated with coronary heart disease. In addition, it appears to be an independent risk factor for coronary heart disease. These risks increase according to the degree and duration of obesity and the distribution of body fat — upper body (abdominal) fat increasing risk more than lower body (gluteal or femoral) fat. Weight reduction has been shown to reduce high blood pressure and high blood cholesterol. Most obese individuals who achieve a more desirable body weight improve their cholesterol profile, achieving a decrease in both total blood cholesterol and LDL (low density lipoprotein) cholesterol.

Some studies have found an association between overweight and increased risk for several cancers, especially cancer of the uterus and breast. In addition, overweight increases the risk for gallbladder disease.

More than a quarter of American adults are overweight. Black women age 45 and above have the highest prevalence, about 60 per cent. Although evidence suggests a genetic component to the tendency of many people to become overweight, patterns of dietary caloric intake and energy expenditure play a key role. Sustained and long-term efforts to reduce body weight can best be achieved as a result of improving energy bal-

ance by reducing energy consumption and raising energy expenditure through physical activity and exercise.

Maintenance of desirable body weight throughout the lifespan requires a balance between energy (calorie) intake and expenditure. Weight control may be facilitated by decreasing energy intake, especially by choosing foods relatively low in calories, fats, and sugars, and by minimizing alcohol consumption. Energy expenditure can be enhanced through regular physical activities such as daily walks or by jogging, bicycling, or swimming at least three times a week for at least 20 minutes.

• *Complex carbohydrates and fiber:* Increase consumption of whole grain foods and cereal products, vegetables (including dried beans and peas), and fruits.

Dietary patterns emphasizing foods high in complex carbohydrates and fiber are associated with lower rates of diverticulosis and some types of cancer. The association shown in epidemiologic and animal studies between diets high in complex carbohydrates and reduced risk for coronary heart disease and diabetes mellitus is, however, difficult to interpret. The fact that such diets tend also to be lower in energy and fats, especially saturated fat and cholesterol, clearly contributes to this difficulty. Some evidence from clinical studies also suggests that water-soluble fibers from foods such as oat bran, beans, or certain fruits are associated with lower blood glucose and blood lipid levels. Consuming foods with dietary fiber is usually beneficial in the management of constipation and diverticular disease.

While inconclusive, some evidence also suggests that an overall increase in intake of foods high in fiber might decrease the risk for colon cancer. Among several unresolved issues is the role of the various types of fiber, which differ in their effects on water-holding capacity, viscosity, bacterial fermentation, and intestinal transit time.

Other food components associated with decreased cancer risk are commonly found in diets high in whole grain cereal products containing complex carbohydrates and fiber. In addition, some epidemiologic evidence suggests that frequent consumption of vegetables and fruits, particularly dark green and deep yellow vegetables and cruciferous vegetables (such as cabbage and broccoli), may lower risk for cancers of the lung and bladder as well as some cancers of the alimentary tract. However, the specific components in these foods that may have protective effects

have not yet been established. Current evidence suggests the prudence of increasing consumption of whole grain foods and cereals, vegetables (including dried beans and peas), and fruits.

• *Sodium:* Reduce intake of sodium by choosing foods relatively low in sodium and limiting the amount of salt added in food preparation and at the table.

Studies indicate a relationship between a high sodium intake and the occurrence of high blood pressure and stroke. Salt contains about 40 per cent sodium by weight and is used widely in the preservation, processing, and preparation of foods. Although sodium is necessary for normal metabolic function, it is consumed in the United States at levels far beyond the 1.1 to 3.3 grams per day found to be as safe and adequate for adults by the National Research Council. Average current sodium intake for adults in the United States is in the range of four to six grams per day.

Blacks and persons with a family history of high blood pressure are at greater risk for this condition. While some people maintain normal blood pressure levels over a wide range of sodium intake, others appear to be "salt sensitive" and display increased blood pressure in response to high sodium intakes.

Although not all individuals are equally susceptible to the effects of sodium, several observations suggest that it would be prudent for most Americans to reduce sodium intake. These include the lack of a practical biological marker for individual sodium sensitivity, the benefit to persons whose blood pressures do rise with sodium intake, and the lack of harm from moderate sodium restriction.

Processed foods provide about a third or more of dietary sodium. Because about another third of the sodium consumed by Americans is added by the consumer, much can be done to reduce sodium consumption by using less salt at the table and substituting alternative flavoring such as herbs, spices, and lemon juice in the preparation of foods. In addition, choices can be made of foods modified to lower sodium content and less frequent choices could be made of foods to which sodium is added in processing and preservation.

• *Alcohol:* To reduce the risk for chronic disease, take alcohol only in moderation (no more than two drinks a day), if at all. Avoid drinking any alcohol before or while driving, operating ma-

chinery, taking medications, or engaging in any other activity requiring judgment. Avoid drinking alcohol while pregnant.

Alcohol is a drug that can produce addiction in susceptible individuals, birth defects in some children born to mothers who drink alcohol during pregnancy, impaired judgment, impaired ability to drive automobiles or operate machinery, and adverse reactions in people taking certain medications. In addition, alcohol abuse has been associated with disrupted family functioning, suicides, and homicides.

Excessive use of alcohol is also associated with liver disease, some types of cancer, high blood pressure, stroke, and disorders of the heart muscle. Extensive epidemiologic and clinical evidence has identified alcohol consumption as the principal cause of liver cirrhosis in the United States, at least in part as a result of the direct toxic effects of alcohol on the liver. Smoking and alcohol appear to act synergistically to increase the risk for cancers of the mouth, larynx, and esophagus. Less conclusive and somewhat conflicting evidence suggests a role of alcohol in other types of cancers such as those of the liver, rectum, breast, and pancreas.

Studies indicate a direct association between increased blood pressure and the consumption of alcohol at levels beyond about two drinks* daily. Extremely excessive alcohol consumption is associated with cardiomyopathy. Alcohol consumption by the mother during pregnancy has also been associated with fetal malformations.

Although consumptions of up to two drinks per day has not been associated with disease among healthy men and nonpregnant women, surveys suggest that at least nine per cent of the total population consumes two or more drinks per day and those in this group need to reduce their alcohol consumption. A threshold level of safety for alcohol intake during pregnancy has not been established. Thus, pregnant women and women who may become pregnant should avoid drinking alcohol.

Other Issues for Some People

- **Fluoride:** Community water systems should contain fluoride at optimal levels for prevention of tooth decay. If such water is not available, use other appropriate sources of fluoride.

* One drink is defined as a 12 ounce beer, a 5 ounce glass of wine, or 1½ fluid ounces (one jigger) of distilled spirits, each of which contains about 1 ounce of alcohol.

The most efficient means of making fluoride available to the general public to reduce dental disease is through drinking water. Numerous epidemiologic and clinical studies have attested to the efficacy, safety and cost-effectiveness of systemic fluoride in the prevention of tooth decay. Lifetime use of water containing an optimal fluoride concentration of approximately one part per million has been shown to reduce the prevalence of dental caries by more than 50 per cent. Water fluoridation is considered one of the most successful public health efforts introduced in the United States.

For children living in areas with inadequate concentrations of fluoride in the water, supplementary fluoride sources should be used at dosages that depend on the fluoride content of the local water supply and the age of the child. The effectiveness of prenatal fluoride administration, however, is uncertain because clinical studies of its effects on subsequent caries incidence have been equivocal. Excessive fluoride should be avoided because it may cause mottling of developing teeth.

- **Sugars:** Those who are particularly vulnerable to dental caries (cavities), especially children, should limit their consumption and frequency of use of foods high in sugars.

Although genetic, behavioral, and other dietary factors also influence dental health, the major role of sugars in promotion of tooth decay is well established from animal, epidemiologic, clinical, and biochemical studies. Newly erupting teeth are generally more vulnerable to decay than mature teeth.

Research has shown that three conditions must exist for the formation of dental caries: the presence of fermentable carbohydrate, acid-producing bacteria, and a susceptible tooth. Caries-producing bacteria metabolize a range of sugars (glucose, fructose, maltose, lactose, and sucrose) to acids that demineralize teeth. The unique role of sucrose (common table sugar) in dental caries is related to its special ability to be converted by these bacteria into long, complex molecules that adhere firmly to teeth and form plaque.

The most important diet-related interventions are fluoridation of drinking water, or the use of other means of fluoride administration, and control of intake of sugars. While fluoride is the most important factor overall in dental caries prevention, reduction in the frequency of consumption and in the quantity of sugar-rich foods in the

diet will also help reduce decay. Sticky sweet foods that adhere to the teeth are more cariogenic than those that wash off quickly. The longer cariogenic foods remain in the mouth, the more they are likely to increase the initiation and progression of tooth decay.

- **Calcium:** Adolescent girls and adult women should increase consumption of foods high in calcium, including low-fat dairy products.

Inadequate dietary calcium consumption in the first three to four decades of life may be associated with increased risk for osteoporosis in later life. Osteoporosis, a chronic disease characterized by progressive loss of bone mass with aging, occurs in both women and men, although postmenopausal women are twice as likely as men to have severe osteoporosis with consequent bone fractures. Evidence shows that chronically low calcium intake, especially during adolescence and early adulthood, may compromise development of peak bone mass. In postmenopausal women, the group at highest risk for osteoporosis, estrogen replacement therapy under medical supervision is the most effective means to reduce the rate of bone loss and risk for fractures. Maintenance of adequate levels of physical activity and cessation of cigarette smoking have also been associated with reduced osteoporosis risk.

Although the precise relationship of dietary calcium to osteoporosis has not been elucidated, it appears that higher intakes of dietary calcium could increase peak bone mass during adolescence and delay the onset of bone fractures later in life. Thus, increased consumption of foods rich in calcium may be especially beneficial for adolescents and young women. Food sources of calcium consistent with other dietary recommendations in this Report include low-fat dairy products, some canned fish, certain vegetables, and some calcium-enriched grain products.

- **Iron:** Children, adolescents, and women of childbearing age should be sure to consume foods that are good sources of iron, such as lean red meats, fish, certain beans, and iron enriched cereals and whole grain products. This issue is of special concern for low-income families.

Dietary iron deficiency is responsible for the most prevalent form of anemia in the United States. Iron deficiency hampers the body's ability to produce hemoglobin, a substance needed to carry

oxygen in the blood. A principal consequence of iron deficiency is reduced work capacity, although depressed immune function, changes in behavior, and impaired intellectual performance may also result. Because of the serious consequences of iron deficiency, continual monitoring of the iron status of individuals at high risk — particularly children from low-income families, adolescents, and women of childbearing age — is vital, as is treatment of those identified to be iron deficient.

Proper infant feeding — preferably breast-feeding, otherwise use of iron-fortified formula — is the most important safeguard against iron deficiency in infants. Among adolescents and adults, iron intake can be improved by increasing consumption of iron-rich foods such as lean red meats, fish, certain kinds of beans, and iron-enriched cereals and whole grain products. Also, consuming foods that contain vitamin C increases the likelihood that iron will be absorbed efficiently.

Policy Implications: Dietary Guidance

General Public. Educating the public about the dietary choices most conducive to prevention and control of certain chronic diseases is essential. Educational efforts should begin in primary school and continue throughout the secondary grades, and should focus on the dietary principles outlined in this Report — the potential health benefits of eating a diet that is lower in fat (especially saturated fat) and rich in complex carbohydrates and fiber. The importance of adequate physical activity should also be stressed. Efforts should continue throughout each stage of life to promote the principles outlined in the *Dietary Guidelines for Americans*.

Special Populations. A disproportionate burden of diet-related disease is borne by subgroups in our population. Black Americans, for example, have higher rates of high blood pressure, strokes, diabetes, and other diseases associated with obesity (but lower rates of osteoporosis) than the general population. Some groups of Native Americans exhibit the highest rates of diabetes in the world. Pregnant and lactating women also have special nutritional needs. Particular effort should be made to identify and remove the barriers to optimal health and nutritional status in such high-risk groups, using methods that take into consideration their diverse cultural backgrounds.

Many older persons suffer from chronic dis-

eases that can reduce functional independence; many take multiple medications that may adversely interact with nutrients. Sound public education directed toward this group — and professional education directed toward individuals who care for older Americans — should focus on dietary means to reduce risk factors for chronic disease, to promote functional independence, and to prevent adverse consequences of use of medications.

Health Professionals. Improved nutrition training of physicians and other health professionals is needed. Training should emphasize basic principles of nutrition, the role of diet in health promotion and disease prevention, nutrition assessment methodologies and their interpretation, therapeutic aspects of dietary intervention, behavioral aspects of dietary counseling, and the role of dietitians and nutritionists in dietary counseling of patients.

Programs and Services

Food Labels. Food labeling offers opportunities to inform people about the nutrient content of foods so as to facilitate dietary choices most conducive to health. Food manufacturers should be encouraged to make full use of nutrition labels. Labels of processed foods should state the content of calories, protein, carbohydrate, fats, cholesterol, sodium, and vitamins and minerals. To the extent permitted by analytical methods, manufacturers should disclose information where appropriate on the content of saturated and unsaturated fatty acids and total fiber in foods that normally contain them. Descriptive terms such as "low calorie" and "sodium reduced" in compliance with the Food and Drug Administration's regulations for food labeling may also be helpful, and the expanded use of these terms should be encouraged.

Nutrition Services. Health care programs for individuals of all ages should include nutrition services such as, when appropriate, nutrition counseling for individuals or groups, interpretation and implementation of prescribed therapeutic diets tailored to individual food preferences and lifestyle, referral to appropriate community services and food assistance programs, monitoring of progress, and appropriate followup. These services should routinely incorporate assessment of nutritional status and needs based on established criteria to identify individuals with nutritional risk factors who would profit

from preventive measures and those with nutritional disorders who need remedial care.

Food Services. Lack of access to an appropriate diet should not be a health problem for any American. Wherever food is served to people or provided through food assistance programs, it should reflect the principles of good nutrition stated in this Report. Whether served in hospitals, schools, military installations, soup kitchens, day care centers, or nursing homes, or whether delivered to homes, food service programs offer important opportunities for improving health and providing dietary education. Such programs should pay special attention to the nutritional needs of older people, pregnant women, and children, especially those of low income or other special dietary needs. Because a large proportion of the population takes meals in restaurants and convenience food facilities, improvements in the overall nutritional balance of the meals served in such places can be expected to contribute to health benefits.

Food service programs should also take particular care to ensure that special diets lower in fat, especially saturated fat, are provided to people with elevated blood cholesterol, heart disease, or diabetes; that diets low in sodium are provided to individuals with high blood pressure; and that protein-restricted diets are made available to people with end-stage kidney disease.

Food Products. The public would benefit from increased availability of foods and food products low in calories, total fat, saturated fat, cholesterol, sodium, and sugars, but high in a variety of natural forms of fiber and, perhaps, certain minerals and vitamins. Food manufacturers can contribute to improving the quality of the American diet by increasing the availability of palatable, easily prepared food products that will help people to follow the dietary principles outlined here. Because the public is becoming increasingly conscious of the role of nutrition in health, development of such products should also benefit the food industry.

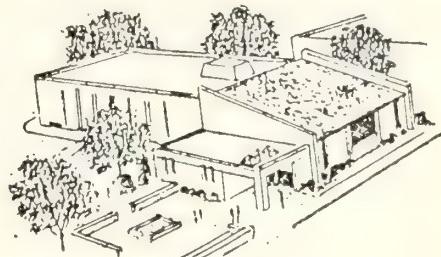
Research and Surveillance

Impressive evidence already links nutrition to chronic disease. However, much more information is needed to continue to identify changes in the national diet that will lead to better health for the Nation. Gaps in our knowledge of nutrition suggest future research and surveillance needs. Examples are:

- The role of specific dietary factors in the etiology and prevention of chronic diseases.
- The childhood dietary pattern that will best prevent later development of chronic diseases.
- The effects of maternal nutrition on the health of the developing fetus.
- The nutrient and energy requirements of older adults.
- How nutrient requirements translate into healthful dietary patterns.
- The development of biochemical markers of dietary intake to monitor better the effects of dietary intervention.
- The identification of effective educational methods to translate dietary recommendations into appropriate food choices.
- The establishment of a nutrition surveillance system that will enhance the monitoring of population-specific and State-specific trends in the occurrence of nutrition-related risk factors and conditions.

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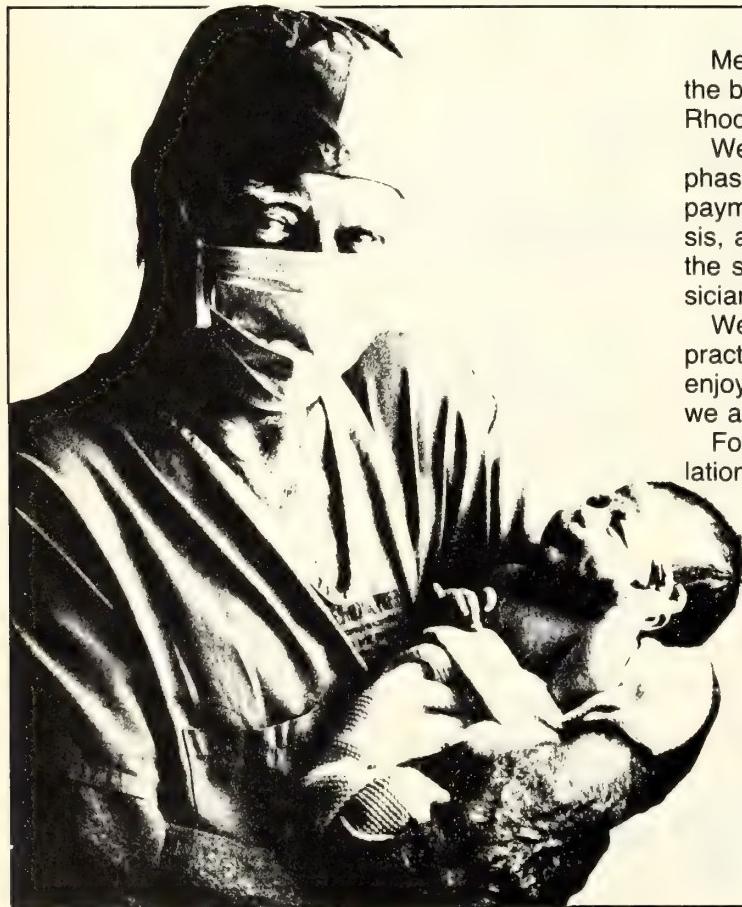
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It is rarely desirable to include a complete review of the literature in the references. An alphabetized bibliography is to be used only when the listing is of books suggested for supplementary reading.



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● Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

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Therapy-related adverse reactions are uncommon. Those reported include

● Gastrointestinal (mostly diarrheal): 2.5%

● Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.

● Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthritis, and frequently, fever]: 1.5%, usually subsides within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

● Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

● As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

● Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertension, dizziness, and somnolence have been reported.

● Other: eosinophilia, 2%; genital pruritis or vaginitis, less than 1%; and, rarely, thrombocytopenia.

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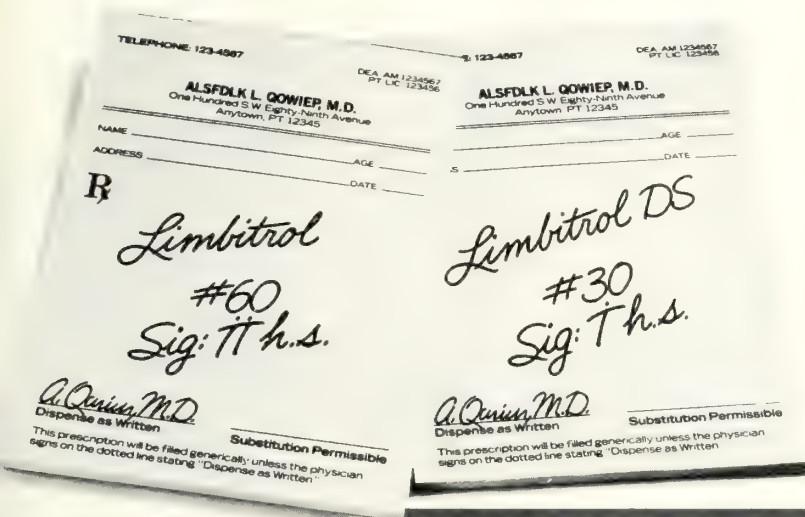
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References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Feighner VP, et al: Psychopharmacology 61:217-225, Mar 22, 1979.

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Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

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Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs: **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. **Neurologic:** Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extra-pyramidal symptoms, syncope, changes in EEG patterns. **Anticholinergic:** Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. **Allergic:** Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus. **Hematologic:** Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. **Endocrine:** Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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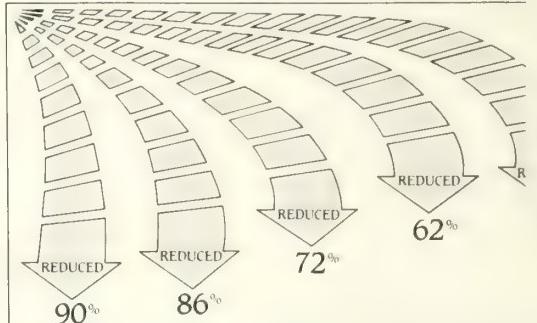
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The Challenge of the Nation's First Comprehensive AIDS Law

Jeffrey F. Chase-Lubitz, Esq.
Jeffery M. Alexander, Esq.

Cover: This month's JOURNAL is a special issue devoted to the new Rhode Island AIDS legislation, scheduled to take effect in January of 1989.

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There are no known contraindications to the use of sucralfate.

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE

There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

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CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1712-49). Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 bracketed by C's on the other.

Issued 1/87

Reference:

- Eliakim R, Ophir M, Rachmilewitz D: *J Clin Gastroenterol* 1987;9(4):395-399.

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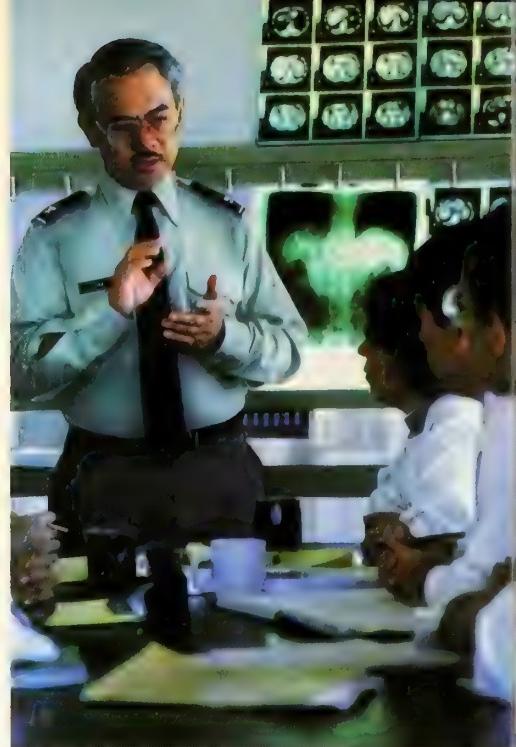
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EDITORIAL

A Look Back: 1988 AIDS Legislation and the Role of RIMS

Every physician in Rhode Island is aware that the state legislature passed a bill last Spring concerning acquired immunodeficiency syndrome (AIDS). Since many segments of the public were interested and the issues surrounding this disease so controversial, the public hearings at the State House, especially those in the House of Representatives, were among the most contentious and lengthy on record. The Rhode Island Medical Society (RIMS) presented testimony at these hearings. The process by which RIMS studied this bill and its subsequent approach before the legislature are the subjects of this commentary.

Before discussing this matter in any detail, several points are worth stressing. First, the appearance of a highly lethal infectious disease is not an isolated event in medical history. While some of the pathophysiological mechanisms that impair the host's immune system are, in fact, without precedent, many epidemics occurring throughout history have been both highly communicable and untreatable. It was the appearance of these intractable illnesses that led to the establishment of scientific principles underlying methods of infection control and the disciplines of epidemiology and public health. The nature of the present AIDS epidemic should not cause the medical profession, in response to an aroused and alarmed public, to depart from classically derived principles of investigation, discussion, and treatment. These principles, however, are tested to the utmost when thorny questions, such as mandatory testing, arise in today's society.

A major problem RIMS had to confront was the difficulty of establishing positions on a piece of legislation which, reflecting the give and take of the legislative process, seemingly changed daily.

Another difficulty stemmed from the paucity of empirical data to corroborate various positions. "No data!" was the recurring complaint. Physicians are accustomed to working in a milieu in which the facts are not totally available. However, such an environment could easily create inequities and distortions in the process of stretching the delicate strands of medical logic into the iron realities of law.

RIMS also wrestled with problems engendered by the exceptional degree to which the public and its representatives have stepped into the medical arena and expropriated large areas hitherto considered sacrosanct by physicians. Issues such as which segments of the public are to be tested are now questions being addressed by the legislature and not physicians in isolation. There are precedents for this in matters of public health, but both the scope and extent of the public debate surrounding AIDS, as well as the resultant legislative thrust, are a major encroachment upon traditional medical preserves. It is in just such an environment that strident views coming from any point of the political compass may vitiate reasoned debate. The Rhode Island legislature, a microcosm of society and a reflection of the tumultuous social and political developments of the last several decades, serves appropriately as an outlet for political and social views, but as the source of medical policy it makes most physicians uncomfortable. Physicians fear that the subtlety and nuance of medicine will be lost in the black and white rigidities of legislation. As a result of these concerns, the Medical Society decided it could best serve its members and the public by being an active participant in the legislative debate.

A final point is that much of the controversy

surrounding AIDS has little to do with the usual and customary practice of medicine. This is not to say that questions raised by such issues as informed consent or mandatory testing did not exist previously, but these issues are less medical issues per se than they are unresolved civil and legal questions which reflect the evolution of social thinking in this country. It is interesting that problems which provoke less disagreement, such as AIDS testing for aliens, potentially infected newborns, military recruits, and prisoners relate to those populations in which civil rights issues are muted. If constitutional issues are not prominent, the debate quiets down and both the medical community and public return to a more traditional posture. When RIMS took up the debate last Spring, it became evident that it was leaving "pure medicine" behind and entering the interface between medicine and politics. This, of course, is what modern medical societies must do increasingly in order to meet their obligation to society and to the profession.

Thus, in late fall of 1987, long before the General Assembly convened to debate the AIDS issue, Dr Richard Bertini, past RIMS president, appointed an AIDS advisory committee, which was headed by Dr Herbert Rakatansky. The composition of the group was diverse, consisting of infectious disease specialists, practitioners, academicians, and physicians dealing routinely with AIDS patients. The committee's in-depth discussions touched upon the medical, legal, and ethical issues raised by this daunting disease. When there was no unanimity regarding a particular topic, a vote was taken and the committee adopted the position of the majority, reminiscent of the manner in which the platforms are created by political parties. (Elsewhere in this issue of the *Journal*, the specific positions of the committee are recorded.) After countless hours of enlightened and spirited debate, a comprehensive AIDS policy emerged. In general, this policy affirmed a physician's ethical responsibility to treat AIDS sufferers, outlined instances when mandatory AIDS testing is appropriate (including protecting the health care team), and advocated a physician's right to inform unsuspecting third parties if they have been potentially exposed to the AIDS virus. After the governing body of the Medical Society adopted this policy, RIMS lobbyists approached an influential lawmaker, Senator James D'Ambra, chairman of the Senate Health, Education, and Welfare committee, to sponsor legislation reflecting policies advocated by RIMS.

However, in the midst of a hectic legislative

session, a startling event occurred. H. Denman Scott, MD, Director of the State Department of Health, broke ranks with his own AIDS advisory committee in proposing a sweeping program of mandatory and routine testing for the AIDS virus, citing, among other things, local studies which showed a high prevalence of AIDS infection among certain groups. Within days, the Governor's own AIDS bill was greatly amended to include a full program for testing convicted prostitutes and intravenous (IV) drug users, hospital patients, correctional inmates, marriage applicants, individuals in substance abuse programs, and those seeking prenatal care. Needless to say, confusion reigned when it was revealed that the Governor's bill and the package introduced by Senator James D'Ambra would merge into one Omnibus AIDS Bill. Our wagon, so to speak, was now hitched to a new team of horses.

In the midst of a rancorous debate, the Medical Society scrambled to analyze the impact of the new provisions. At the same time, RIMS staffers were called upon by legislative leaders for assistance in honing a final version of the bill. It was decided to call an emergency meeting of the AIDS advisory committee. Generally, the committee offered support for the Omnibus AIDS bill. However, there were points of disagreement, including the committee's emphatic opposition to a provision that landlords should be allowed to refuse tenants on the basis of the suspicion of AIDS. (This provision was later struck from the bill.) Also, the issues of routine premarital testing and testing in family-planning clinics did not receive support.

One crucial hearing was held by the House Health, Education, and Welfare committee, chaired by Rep Anthony Carnevale. All interested parties presented their views in a truly epic session that lasted well into the night. RIMS along with a number of other medical spokespersons presented testimony. During the hearing a separate bill was introduced in which a zealous legislator attempted to make it illegal for a physician to deny care to anyone suspected of having AIDS,* while at the same time allowing any potentially infected person the right to refuse human immunodeficiency virus (HIV) testing. If only to oppose this version of the bill, the presence of RIMS was critical. Subsequent to the

* As noted earlier in this paper, the Rhode Island Medical Society has declared that physicians are ethically obligated to treat patients with AIDS. However, it is clearly not in the interest of such patients that a reluctant physician be legally compelled to provide care.

hearing, Health Department officials and House and Senate legislators met and hammered out the final version of the bill, a copy of which is also included in this issue.

Overall, it is not difficult to measure the impact RIMS had on the AIDS bill. In every key discussion, public and private, RIMS was a participant, arguing for the need to strike a proper balance between the rights of individual patients and measures necessary to protect the public health. The health care worker section is a direct result of this kind of influence, as is the immunity provision for doctors who warn endangered third parties. Those who consider some aspects of the bill anathema from a medical or civil rights standpoint, should take solace in the fact that it might have been much worse. RIMS was able to mitigate some of the more egregious portions. Those who think the law is weak should realize that it was as strong as a representative body of physicians could make it. Those who dislike the profession of medicine being roughed up in the schoolyard of Rhode Island politics have our sympathy. Again, it makes most physicians apprehensive when medical problems become "legislatalized." However, given the diverse number of disciplines and mindsets encompassed under the term "physician," RIMS performed a difficult task with deliberation and respect for all parties. And, since all legislation is the product of compromise, no one is ever completely satisfied with the result. Yet, members of RIMS can be assured that their concerns were fully and democratically aired through our own AIDS and executive committees, as well as the public hearings held at the statehouse.

There will be much more of this type of activity in our future. The presence of RIMS in the legislature will be necessary and routine, as it attempts to encourage rationality in medicine. It is now being influenced not only by physicians and their organized representatives, but by the legislature as well. The 1989 session of the Rhode Island General Assembly is only two months away!

Boyd P. King, MD
President
Rhode Island Medical Society

Mark Montella
Director of Legislative Affairs
Rhode Island Medical Society

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Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

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- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in

moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.

● Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

● Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions:

(percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:

● Gastrointestinal (mostly diarrhea) 2.5%

● Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.

● Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis) or the above skin manifestations accompanied by arthritis/arthritis, and frequently, fever, 15%.

usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

● Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

● As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

● Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertension, dizziness, and somnolence have been reported.

● Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%, and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology:

● Slight elevations in hepatic enzymes.

● Transient fluctuations in leukocyte count (especially in infants and children).

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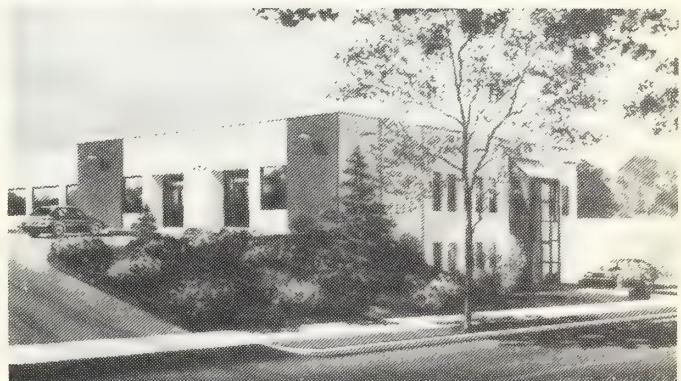
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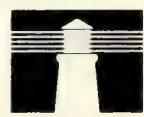
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Rhode Island Medical Society/ Policy Statement on AIDS

Adopted by the Rhode Island Medical Society Council December 16, 1987

Mandatory testing for HIV

Testing for the AIDS virus should be mandatory for donors of blood and blood fractions, organs, and other tissues intended for transplantation in the United States or abroad, for donors of semen or ova collected for artificial insemination, excluding between married couples, for immigrants to the United States, for inmates in federal and state prisons, for military personnel, and for patients who withhold informed consent after their bodily fluids have, in the course of medical treatment, contaminated a health care worker.

Anonymity of HIV test results

Individuals who are found to be seropositive for the AIDS virus should be reported to appropriate public health officials on an anonymous basis with enough information to be epidemiologically significant.

Warning to third parties

Physicians should inform seropositive patients of the dangers posed to individuals with whom they exchange bodily fluids. Physicians should strongly encourage HIV patients to inform their sexual partners or IV needle partners of their seropositivity. If, after taking these steps, a physician is convinced that an endangered third party has not been warned, the physician may, with immunity, notify the third party.

Thus, Chapter 37.3 of the General Laws of Rhode Island, the Health Care Information Act, should be amended to contain:

37.3-4 Limitations on disclosure

- b) No consent for release or transfer of confidential health care information is required in the following situation:
 - (19) By a physician to an individual the health care provider suspects may have been exposed to the AIDS virus.

The principle of informed consent

There should be no testing for HIV infection without prior written informed consent. However, there are instances when adherence to this principle is either unworkable or medically injudicious. Thus, at the present time, the committee recognizes three exemptions: 1) the Rhode Island Blood Bank; 2) alternate testing sites established by the Department of Health; 3) testing of infants under the age of two.

Placing HIV test results on the medical record

As with any diagnostic test, the placement on the medical record of a patient's HIV status is essential for the proper treatment of the patient. Prior to testing, the individual should be informed that the results will become part of the medical record. If the patient objects, and it is feasible, he/she should be encouraged to submit to testing at an alternate testing site.

Seropositivity and insurance

I. Life insurance

Life insurance companies require a physical examination of all potential enrollees in order to assess properly the health risk of the individual, and they routinely deny coverage on the basis of existing health problems. Therefore, it is reasonable for a company to require an HIV test as part of the physical examination. However, the individual must give written informed consent before a test is administered. There should be no HIV testing for individuals enrolled in group life insurance plans.

In addition, protocols should be implemented concerning the notification of an individual who has tested positive for HIV infection. The committee recommends that insurance companies notify individuals through a physician who has experience counseling seropositive patients.

II. Health insurance

The Committee affirms that AIDS and ARC

patients should have access to health insurance. They also recognize that, as with life insurance, individuals are denied health coverage because of many pre-existing conditions.

Thus, for individual policies, it is reasonable to expect that an insurer may require an HIV test. If an individual is seropositive, the health insurance company must comply with the notification protocol already outlined. HIV testing for individuals insured through groups should not be allowed, since the risks are spread throughout the group.

A fund for indigent AIDS sufferers utilizing revenues from the public and private sectors should be established to subsidize the patient's existing insurance premium. In addition, the state should explore ways to encourage the establishment of high risk insurance pools for AIDS patients who are without health coverage.

Physicians' ethical responsibility to treat HIV patients

The Medical Society endorses the pronouncement of the AMA's Council on Ethical and Judicial Affairs concerning the responsibilities a physician has to AIDS patients.

All AIDS patients require competent, compassionate treatment. It is unethical for a physician to refuse to treat an AIDS patient within his/her realm of competence. Moreover, "physicians should respond to the best of their abilities in cases of emergency, and should not abandon patients whose care they have undertaken" (AMA Council on Ethical and Judicial Affairs). Physicians who are unable to provide appropriate care to AIDS patients should "make the appropriate referral to those physicians or facilities that are equipped to provide such services."

HIV testing of health care personnel

Recognizing that there may be instances when a health care worker poses a threat to patients, the Medical Society endorses the statement of the Council on Ethical and Judicial Affairs concerning health care workers who are seropositive, which noted that "patients are entitled to expect that their physicians will not increase their exposure to the risk of contracting an infectious disease, even minimally." Physicians who are infected should not perform procedures that will risk contaminating the patient.

If a patient has been contaminated by a health care worker and the worker refuses to grant informed consent to an HIV test, the test should be mandatory.

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocan® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral α-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocan® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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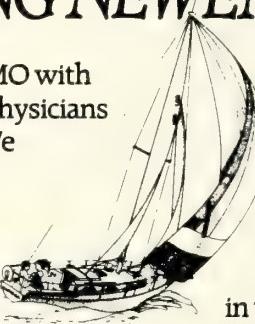
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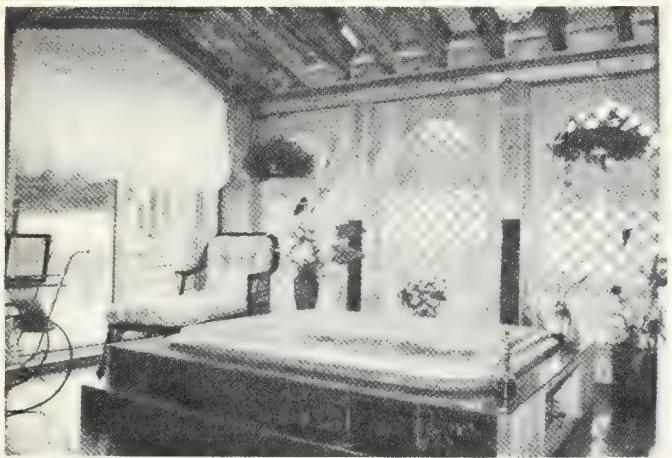
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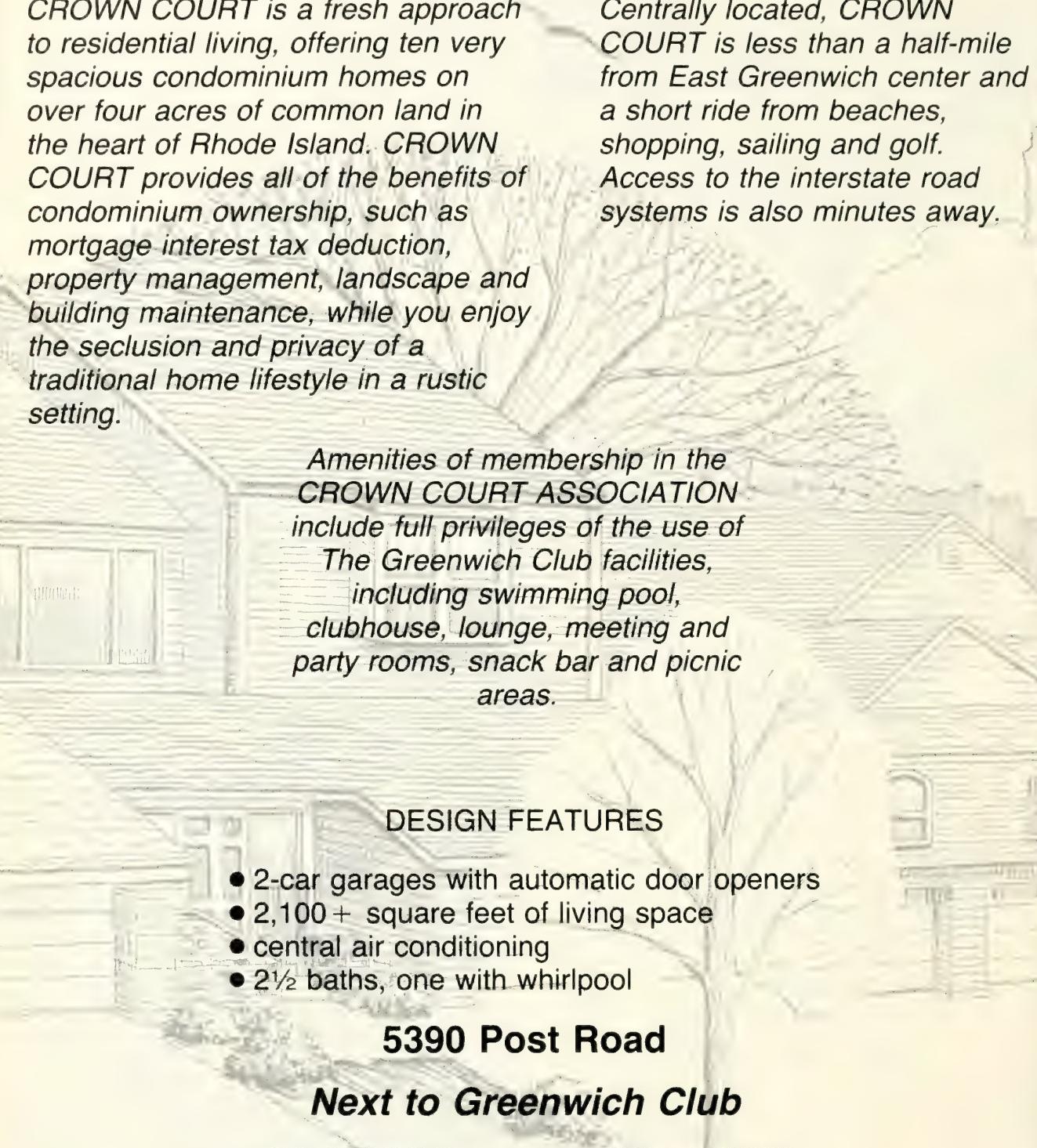
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State of Rhode Island In General Assembly January Session, A.D. 1988

AN ACT RELATING TO HEALTH AND SAFETY — AIDS TESTING, CONFIDENTIALITY AND DISCRIMINATION

Prevention and Suppression of Contagious Diseases

SECTION.

- 23-6-10. Purpose.
- 23-6-11. Definitions.
- 23-6-12. Testing — Requirement for informed consent.
- 23-6-13. Informed consent form.
- 23-6-14. Exceptions.
- 23-6-15. Reasonable effort to secure consent.
- 23-6-16. Due process — Right to bring suit.

SECTION.

- 23-6-17. Confidentiality — Disclosure of test results.
- 23-6-18. Protection of records.
- 23-6-19. Penalties and remedies.
- 23-6-20. Notification of disclosure.
- 23-6-21. Protection of public health.
- 23-6-22. Discrimination prohibited.
- 23-6-23. Administrative relief.
- 23-6-24. Insurance exemption.

Introduced By: Senators D'Ambra, Carlin, Bevilacqua, Hanson, Goldberg, Donelan, Walton and Reed

Date Introduced: April 6, 1988

Referred To: Senate Committee on Health, Education and Welfare

23-6-10. Purpose. [Effective January 1, 1989.]

— The purpose of §§23-6-10 through 23-6-24 is to protect the public against transmission of the AIDS virus, and to protect persons who are infected with the AIDS virus from discrimination.

23-6-11. Definitions. [Effective January 1, 1989.]

— As used in §§23-6-10 through 23-6-24:
(1) "AIDS" means the medical condition known as Acquired Immune Deficiency Syndrome, caused by infection of an individual by the Human Immunodeficiency Virus (HIV).

(2) "AIDS Test" means any currently medically accepted diagnostic test for determining infection of an individual by the AIDS Virus (HIV).

(3) "Person" means any individual, firm, partnership, corporation, company, association or joint stock association.

(4) "Physician" means a person licensed to practice allopathic or osteopathic medicine pursuant to the provisions of chapter 37 of title 5.

(5) "Services" means health care and social support services.

(6) "Exposure evaluation group" means three (3) impartial health care providers designated to determine if a health care provider has been involved in a significant exposure. No member of the group shall be directly involved in the exposure.

(i) For inpatient services in a licensed health care facility hospital setting the group shall consist of the patient's attending physician, the chief of service and a staff nurse. For other non-in-

patient exposures in a licensed health care facility, the third member of the exposure evaluation group shall be a representative from the employee health office. If the exposure involves the attending physician, another physician shall be designated by the chief of service.

(ii) In any other licensed health care facility or in a private office of a physician the group shall consist of three (3) physicians.

(7) "AIDS Testing and Notification Form" means a standardized form provided by the Rhode Island Department of Health. Said form shall be developed by the department and shall contain the following information:

(i) the public health rationale for AIDS testing;

(ii) the availability and cost of AIDS testing and counseling;

(iii) that test results are confidential with certain exceptions;

(iv) a list of exceptions to confidentiality of test results;

(v) that the test is voluntary and that an informed consent form must be signed before testing;

(vi) that by signing this form the person is only acknowledging that the AIDS test and counseling have been offered.

23-6-12. Testing — Requirement for informed consent. [Effective January 1, 1989.] — Unless otherwise excepted by the provisions of this chapter, no person may be tested for presence of the AIDS virus, where the test result can be identified with a specific individual, unless he or she has given his or her informed consent by his or her signature or that of a parent, guardian, or agent on a written informed consent form specifically relating to such test after discussion of implications of the test with a qualified professional.

23-6-13. Informed consent form. [Effective January 1, 1989.] — The written informed consent form shall include at least the following: (a) the name and signature of the party(s) seeking and consenting to the AIDS test, (b) the name and nature of the test, (c) the reasons for conducting the test, (d) the fact that the test results shall remain confidential except as required by law, and (e) explanation of how test results will affect the tested person's ability to obtain services from the party requesting the test, or those for whom he or she is acting.

23-6-14. Exceptions. [Effective January 1, 1989.] — Notwithstanding the provisions of §§23-6-12 and 23-6-13, a physician may secure a test for the presence of the AIDS virus without in-

formed consent under the following conditions:

(a) When the person to be tested is under one year of age;

(b) When the person to be tested is between one and thirteen (13) years of age and appears to be symptomatic for AIDS;

(c) When the person to be tested is a minor under the care and authority of Rhode Island Department of Children and their Families, and the director of said department certifies that an AIDS test is necessary to secure health or human services for that person;

(d) When a person (the complainant) can document significant exposure to blood or other bodily fluids of another person (the individual to be tested), during performance of the complainant's occupation, providing:

(i) The complainant completes an incident report within forty-eight (48) hours of the exposure, identifying the parties to the exposure, witnesses, time, place and nature of the event;

(ii) The complainant submits to a baseline AIDS test and is negative on that test for the presence of the AIDS virus, within seventy-two (72) hours of the exposure; and

(iii) There has been a significant percutaneous or mucous membrane exposure, i.e., needlestick; bite; splash over open wound, broken skin, or mucous membrane; by blood or body fluids of the person to be tested; of a type and in sufficient concentration to permit transmission of the AIDS virus, if present in those fluids.

(e) In a licensed health care facility in the event that an exposure evaluation group, as defined above, determines that a health care provider has a significant exposure to the blood and/or body fluids of a patient and the patient or the patient's guardian refuses to grant informed consent for an HIV test to determine whether the patient has the AIDS virus, then, if a sample of the patient's blood is available, said blood shall be tested for the AIDS virus:

(i) If a sample of the patient's blood is not otherwise available and the patient refuses to grant informed consent, then the health care worker may petition the superior court for a court order mandating that the test be performed.

(ii) Before a patient or a sample of the patient's blood is required to undergo an HIV test, the health care provider must submit to a baseline AIDS test within seventy-two (72) hours of the exposure.

(iii) No member of the exposure evaluation group who determines that a health care worker has sustained a significant exposure and author-

izes the HIV testing of a patient nor any person or health care facility who relies, in good faith, on the group's determination and performs the test shall have any liability as a result of their actions carried out under this chapter, unless such persons act in bad faith.

(f) In an emergency, where due to a grave medical or psychiatric condition, it is impossible to obtain consent from either the patient or the patient's parent, guardian or agent.

(g) As permitted under §§23-18.5-8 and 23-1-38.

(h) Mandatory testing for Human Immunodeficiency Virus (HIV) conducted pursuant to §§42-56-37, 11-34-9 [11-34-10] and 21-28-4.18.

23-6-15. Reasonable effort to secure consent. **[Effective January 1, 1989.]** — No involuntary testing for the AIDS virus shall take place under any of the exceptions set forth in §23-6-14 until reasonable efforts have been made to secure voluntary informed consent.

23-6-16. Due process — Right to bring suit. **[Effective January 1, 1989.]** — Nothing in this act shall be construed to limit or deprive any person of their right to due process of law, or to bar an action for relief and/or damages before a court of competent jurisdiction.

23-6-17. Confidentiality — Disclosure of test results. **[Effective January 1, 1989.]** — It shall be unlawful for any person to disclose to a third party the result of an individual's AIDS test without the prior written consent of that individual, or in the case of a minor, the minor's parent, guardian or agent on a form that specifically states that HIV test results may be released, except:

(a) A licensed health care facility or laboratory may report test results to a licensed physician, or other authorized medical personnel who requested the test(s) and shall, pursuant to rules and regulations, report to the director of the department of health.

(b) A physician:

(i) May enter AIDS test results in the medical record, as would be the case with any other diagnostic test;

(ii) May notify other health professionals directly involved in care of the individual testing positive on the AIDS test, or to whom that individual is referred for treatment;

(iii) May notify persons exposed to blood or other body fluids of an individual who tests positive for AIDS, pursuant to §23-6-14(d) through (h) above and §23-17-31;

(iv) May notify the director of the department for children and their families, pursuant to §23-

6-14(c); and

(v) May inform third-parties with whom an AIDS-infected patient is in close and continuous contact, including but not limited to a spouse; if the nature of the contact, in the physician's opinion, poses a clear and present danger of AIDS transmission to the third party; and if the physician has reason to believe that the patient, despite the physician's strong encouragement, has not and will not warn the third party, the procedure to be followed by the physician shall be established by the director of the department of health;

(c) As permitted in subsection (b)(1), (2), (5), (6), (8), (9), (10), (11), (12), (13), (14), and (15) of §5-37.3-4 of the Confidentiality of Health Care Information Act, and §40.1-5-26 of the Mental Health Law or as otherwise required by law.

(d) By a health care provider to appropriate persons entitled to receive notification of persons with infectious or communicable diseases pursuant to §§23-5-9 and 23-28.36-2 [23-28.36-3].

23-6-18. Protection of records. **[Effective January 1, 1989.]** — Providers of health care, public health officials, and any other person who maintains records containing information on AIDS test results of individuals, shall be responsible for maintaining full confidentiality of this data, as provided in §23-6-17, and shall take appropriate steps for their protection, including:

(a) Keeping records secure at all times and establishing adequate confidentiality safeguards for any such records electronically stored;

(b) Establishing and enforcing reasonable rules limiting access to these records; and

(c) Training persons who handle records in security objectives and technique.

23-6-19. Penalties and remedies. **[Effective January 1, 1989.]** — The penalties and remedies contained in §5-37.3-9 shall apply to violations of §§23-6-17 and 23-6-18.

23-6-20. Notification of disclosure. **[Effective January 1, 1989.]** — In all cases when an individual's AIDS test results are disclosed to a third party, other than a person involved in the care and treatment of the individual, and except as permitted in subsections (a), (b)(i), (b)(ii), (b)(iv), and (d) of §23-6-17, the person so disclosing shall make reasonable efforts to inform that individual in advance of:

(a) The nature and purpose of the disclosure;

(b) The date of disclosure;

(c) The recipient of the disclosed information.

23-6-21. Protection of public health. **[Effective January 1, 1989.]** — Nothing contained in

§§23-6-10 through 23-6-24 shall bar the director of health from exercising the authority and responsibilities conferred on him by law in protecting the public health.

23-6-22. Discrimination prohibited. [Effective January 1, 1989.] — No person, agency, organization or corporate body may discriminate against a person on the basis of a positive AIDS test result, or perception of same, in housing, employment, the granting of credit, public accommodation, or delivery of services, nor shall an AIDS test be required as a condition of employment, except:

(a) Where nondiscrimination can be shown, on the testimony of competent medical authorities, to constitute a clear and present danger of AIDS virus transmission to others; or

(b) Where laws of the state of Rhode Island may otherwise specifically authorize such exceptions.

23-6-23. Administrative relief. [Effective January 1, 1989.] — Any person who believes that he or she has been unlawfully discriminated against in housing, employment, the granting of credit, public accommodations or delivery of services on the basis of a positive AIDS test, or perception of same, may bring action for administrative relief before the Rhode Island Human Rights Commission; and the said commission may hear said matter and grant relief in such cases.

23-6-24. Insurance exemption. [Effective January 1, 1989.] — (a) *Life insurance.* Sections 23-6-10 through 23-6-23 shall not apply to the offering or sale of life insurance in Rhode Island provided however, that any insurance company offering or selling life insurance within Rhode Island that requires an individual to be tested for infection with human immunodeficiency virus (HIV) or any other identified causative agent of AIDS for purposes of determining insurability shall: (i) give said individual prior written notice of such requirements, and (ii) proceed with such testing only upon the written authorization of the individual or in the event the individual is a minor, the individual's parent or guardian. Notwithstanding anything in §§23-6-10 through 23-6-23 to the contrary, life insurance companies offering or selling life insurance in Rhode Island may otherwise obtain or disclose HIV test results in accordance with §23-6-17(c). Nothing herein shall prohibit such company from collecting data for statistical purposes, so long as the insured is not identified. However, nothing herein shall be construed to permit such insurance company to cancel or refuse to renew a life insurance policy

which by its terms has not lapsed on the basis of a positive AIDS test result.

(b) *Health benefits.* Health benefits shall include accident and sickness, including disability or health insurance, health benefit plans and/or policies, hospital, health or medical service plans or any health maintenance organization plan pursuant to title 27 or otherwise; the provisions of §§23-6-10 through 23-6-23 shall apply to the offer or sale of health benefits in this state by any company regulated under the laws of this state including but not limited to title 27 and chapter 62 of title 42 provided, however, §§23-6-10 through 23-6-23 shall not apply to the following:

(i) individual health benefit policies;

(ii) small group health benefits plans, i.e., groups having fewer than twenty-five (25) employees eligible to participate in an employer sponsored plan, or, in the case of non-employer groups, a group having fewer than twenty-five (25) employees;

(iii) late entrants into any group health benefits plan, regardless of the size of the group. A late entrant shall be defined as any individual who does not enroll into a health plan when first eligible thereunder but who later seeks coverage under the group plan;

(iv) where an individual seeks to become eligible for an amount of group disability income benefit, which benefit would be in excess of the insurer's non-medical maximum as defined under the group plan.

Any such company offering or selling health benefits in this state and regulated under the laws of this state that requires an individual to be tested for infection with HIV or any other identified causative agent of AIDS as permitted in (i) to (iv) above for purposes of determining insurability shall: (i) give said individual prior written notice of such requirements, and (ii) proceed with such testing only upon the written authorization of the individual or in the event the individual is a minor, the individual's parent or guardian. Notwithstanding anything in this chapter to the contrary, companies offering or selling health benefits in this state may otherwise obtain or disclose HIV test results in accordance with §23-6-17(c). Nothing herein shall prohibit such company from collecting data for statistical purposes so long as the insured's name is not identified.

Nothing herein shall be construed to permit any company which offers or sells health benefits in this state to cancel or refuse to renew a health benefit, which has not by its terms lapsed, on the basis of a positive AIDS test result.

(c) There is hereby established a commission to develop and recommend to the legislature a risk pool plan under which all insurers issuing health insurance in the state of Rhode Island shall participate and share a proportion of the risk and cost of insuring people with AIDS.

The commission shall consist of eleven (11) members; three (3) of whom shall be members of the house of representatives, not more than two (2) from the same political party to be appointed by the speaker of the house; two (2) of whom shall be members of the senate, not more than one of whom shall be from the same political party to be appointed by the majority leader; one of whom shall be the director of the department of health, or his or her designee; one of whom shall be the director of the department of business regulation, or his or her designee; two (2) of whom shall be representatives of the insurance community, to be appointed by the governor; and two (2) of whom shall be representatives of Rhode Island Project AIDS, to be appointed by the governor.

The commission shall meet at the call of the speaker, and shall make its report to the legislature on or before February 1, 1989.

23-17-31. Human immunodeficiency virus (HIV) testing — Hospitals. [Effective January 1, 1989.] — Hospital patients in any hospital licensed under this chapter shall be offered testing for human immunodeficiency virus (HIV) unless excluded by regulations developed by the department of health, or unless such test is deemed inappropriate by a physician caring for the patient and so noted in the person's medical record. All testing pursuant to this section shall be performed in accordance with §§23-6-12 and 23-6-13. The identity of the individuals tested under this section shall be maintained only at the hospital site where the sample is drawn, and shall not be released except as provided by statute. Each person who is offered such a test and counseling shall be provided with an "AIDS Testing and Notification Form" which he or she shall sign and date in acknowledgment of said offer.

The department of health shall be responsible for reasonable costs associated with performing and reporting the results of the HIV tests.

All persons tested under this section shall be provided pretest and post-test counseling, and the department of health shall define in regulation the nature and scope of the counseling; provided, however, that said counseling shall be in accordance with acceptable medical standards.

The department of health will either provide

or pay for all pretest and post-test counseling. It will negotiate with the hospitals concerning incremental costs associated with pretest and post-test counseling and will provide reasonable reimbursement of these costs or provide the services themselves in the case of post-test counseling.

23-11-17. Human immunodeficiency virus (HIV) testing. [Effective January 1, 1989.] — The physician or health care provider attending any person for a suspected sexually transmitted disease shall offer testing for human immunodeficiency virus (HIV). All testing pursuant to this section shall be performed in accordance with §§23-6-17 and 23-6-18. The identity of the individuals tested under this section shall be maintained only at the site where the sample is drawn, and shall not be released except as otherwise provided by statute.

Each person who is offered such a test and counseling shall be provided with an "AIDS Testing and Notification Form" which he or she shall sign and date in acknowledgment of said offer. The department of health shall be responsible for costs associated with performing and reporting the results of the HIV tests, including the reasonable costs of pretest and post-test counseling. Such reasonable costs shall be negotiated and specified by contract.

All persons tested under this section shall be provided pretest and post-test counseling in accordance with regulations adopted by the department of health; provided, however, that said counseling shall be in accordance with acceptable medical standards.

23-13-19. Human immunodeficiency virus (HIV) testing. [Effective January 1, 1989.] — Every physician or health care provider attending any person for prenatal care or family planning services shall offer testing for human immunodeficiency virus (HIV) unless deemed inappropriate by the physician. All testing pursuant to this section shall be performed in accordance with §§23-6-12 and 23-6-13. The identity of the individuals tested under this section shall be maintained only at the site where the sample is drawn and shall not be released except as otherwise provided by statute. Each person who is offered such a test and counseling shall be provided with an "AIDS Testing and Notification Form" which he or she shall sign and date in acknowledgment of said offer. The department of health shall be responsible for reasonable costs associated with performing and reporting the results of the HIV tests including the reasonable costs of pretest and post-test coun-

seling. Such reasonable costs shall be negotiated and specified by contract.

All persons tested under this section shall be provided pretest and post-test counseling in accordance with regulations adopted by the department of health; provided however that said counseling shall be in accordance with acceptable medical standards.

40.1-24-20. Human immunodeficiency virus (HIV) testing — Facilities for drug abusers. [Effective January 1, 1989.] — Every physician or health care provider attending any person for any service offered at a facility for intravenous drug users, shall offer testing for human immunodeficiency virus (HIV) unless deemed inappropriate by the physician. All testing pursuant to this section shall be performed in accordance with §§23-6-17 and 23-6-18. The identity of the individuals tested under this section shall be maintained only at the site where the sample is drawn, and shall not be released except as otherwise provided by statute.

Each person who is offered such a test and counseling shall be provided with an "AIDS Testing and Notification Form" which he or she shall sign and date in acknowledgment of said offer.

The department of health shall be responsible for reasonable costs associated with performing and reporting the results of the HIV tests, including the costs of pretest and post-test counseling. Such reasonable costs shall be negotiated and specified by contract.

All persons tested under this section shall be provided pretest and post-test counseling in accordance with regulations adopted by the department of health; provided, however, that said counseling shall be in accordance with acceptable medical standards.

Section 6. Section 15-2-3 of the General Laws in chapter 15-2 entitled "Marriage Licenses" is hereby amended to read as follows:

15-2-3. Physical examination and blood test required. — except as otherwise provided in section 15-2-10 no license shall be issued by such town or city clerk until there shall be in the possession of such town or city clerk a statement or statements, upon a form provided by the department of health, signed by a licensed physician that each applicant has submitted to a physical examination, a Wasserman or Kahn or other similar standard laboratory blood test and that, in the opinion of such physician, the person is not infected with syphilis or gonorrhea in any stages of these diseases in which they may become communicable, and such statements shall be ac-

companied by a record of the standard laboratory blood tests, which record shall contain the exact name and address of such applicant. All female applicants shall complete a rubella test approved by the department of health prior to the issuance of a license. Said rubella test shall not be required of women fifty-five (55) years, or older, those previously immunized or tested as evidence by a physician's certificate, those unable to bear children or whose pregnancy at the time of application is certified by a physician. A standard laboratory blood test shall be a laboratory test for syphilis approved by the department of health and shall be performed by said department, on request of a licensed physician and upon payment of a reasonable charge therefor, or at a laboratory approved by it, such test to be made not more than forty (40) days before the issuance of the marriage license. The physician or health care provider shall offer testing for human immunodeficiency virus (HIV). All testing pursuant to this section shall be performed in accordance with the sections 23-6-17 and 23-6-18. The identity of the individuals tested under this section shall be maintained only at the site where the sample is drawn, and shall not be released except as otherwise provided by statute.

Each person who is offered such a test and counseling shall be provided with an "AIDS Testing and Notification Form" which he/she shall sign and date in acknowledgement of said offer.

The department of health shall be responsible for reasonable costs associated with performing and reporting the results of the HIV tests. The department of health will provide pretest and post-test educational materials and provide post-test counseling for HIV positive persons.

All persons tested under this section shall be provided pretest and post-test counseling in accordance with regulations adopted by the department of health; provided, however, that said counseling shall be in accordance with acceptable medical standards.

Section 7. Chapter 42-56 of the General Laws entitled "Department of Corrections" is hereby amended by adding thereto the following Sections:

42-56-37. Human Immunodeficiency Virus (HIV) testing — Every person who shall be committed to the adult correctional institution to answer for any criminal offense, after conviction, shall be required to be tested for Human Immunodeficiency Virus (HIV). No consent for such testing shall be required from the person being tested, nor shall this test be subject to waiver. In

addition, periodic testing for Human Immunodeficiency Virus (HIV), including testing at the time of release and when deemed appropriate by a physician, shall be required. No consent on the part of the person being tested shall be required.

All such inmates shall be provided appropriate pretest and post-test counseling in accordance with accepted medical standards. No inmate shall be punished, or denied recreation privileges solely on the basis of a positive test result. However, the department of corrections shall take steps as are reasonable to prevent persons testing positive for Human Immunodeficiency Virus (HIV) from infecting other inmates and/or correctional staff. Inmates who develop AIDS or AIDS related complex shall be entitled to all reasonable medical treatment available for their illness.

The department of corrections shall institute a comprehensive AIDS education and drug treatment program for inmates and staff at all of its facilities. The mandatory testing required by this section shall commence only upon certification by the department of health that counseling resources are in place.

Section 8. Chapter 11-34 of the General Laws entitled "Prostitution and Lewdness" is hereby amended by adding thereto the following section:

11-34-10. Human Immunodeficiency Virus (HIV) — Any person convicted of a violation of any provisions of chapter 11-34 shall be required to be tested for Human Immunodeficiency Virus (HIV). No consent for such testing shall be required.

The department of health shall be responsible for reasonable costs associated with performing and reporting the results of the HIV tests, including the costs of pretest and post-test counseling.

All persons tested under this section shall be provided pretest and post-test counseling in accordance with regulations adopted by the department of health; provided, however, that said counseling shall be in accordance with acceptable medical standards.

Section 9. Chapter 21-28 of the General Laws entitled "Uniform Controlled Substances Act" is hereby amended by adding thereto the following Section:

21-28-4.20. Human Immunodeficiency Virus (HIV) — Testing. — Any person convicted of possession of any hypodermic instrument associated with intravenous drug use shall be required to be tested for Human Immunodefi-

ciency Virus (HIV). No consent for such testing shall be required.

The department of health shall be responsible for reasonable costs associated with performing and reporting the results of the HIV tests, including the costs of pretest and post-test counseling.

All persons tested under this section shall be provided pretest and post-test counseling in accordance with regulations adopted by the department of health; provided, however, that said counseling shall be in accordance with acceptable medical standards.

Section 10. Chapter 28-20 of the General Laws entitled "Division of Occupational Safety" is hereby amended by adding thereto the following Section:

28-20-4.1. Adoption of regulations pertaining to HIV and Hepatitis. — The division of occupational safety of the department of labor shall adopt the latest regulations of the federal occupational safety and health administration (OSHA) as they pertain to the human immunodeficiency virus (HIV) and hepatitis and shall in consultation with the department of health provide for the enforcement of such regulations for appropriate public sector employees.

Section 11. Section 23-1-37 of the General Laws in Chapter 23-1 entitled "Department of Health" is hereby repealed in its entirety.

Section 12. Severability of Provisions. — If any provision of this act or any rule or regulation made thereunder, or the application thereof to any person or circumstance, is held invalid by a court of competent jurisdiction, the remainder of the act, rule, or regulation and the application of such provision to other persons or circumstances shall not be affected thereby. The invalidity of any section or sections or parts of any section or sections of this act shall not affect the validity of the remainder of the act.

Section 13. This act shall take effect on January 1, 1989.

RS1092/SUB B/5

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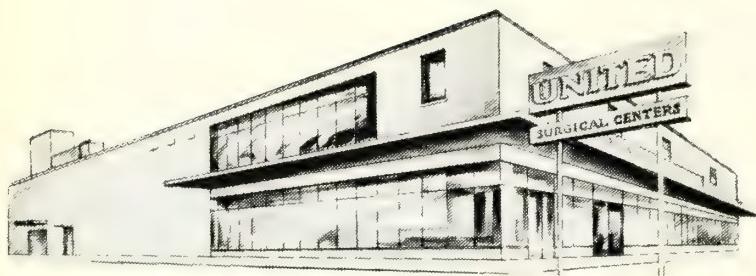
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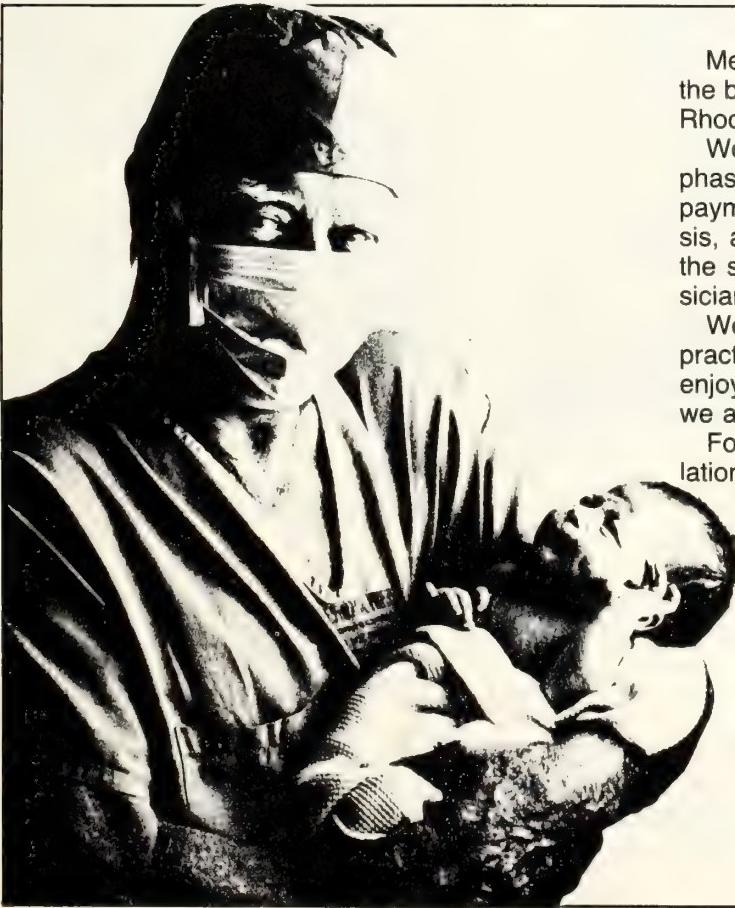
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The New Rhode Island AIDS Statute

The Challenge of the Nation's First Comprehensive AIDS Law

Jeffrey F. Chase-Lubitz, Esq.
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On January 1, 1989, Rhode Island will implement the most comprehensive AIDS statute in the nation. Entitled the AIDS Testing, Confidentiality and Discrimination Act (the Act), this expansive legislation addresses many of the controversial aspects of the AIDS crisis. The Act is of particular importance to Rhode Island's health care facilities and physicians, who bear most of the responsibility for carrying out the Act's requirements.

The Act mandates that health care providers offer human-immunodeficiency virus (HIV) testing to certain individuals and delineates testing and consent procedures. It creates a special procedure permitting health care workers to discover whether they have been exposed to the AIDS virus and establishes rules regarding when and to whom test results may be disclosed. Under certain circumstances, the Act allows physicians to warn individuals with whom they suspect AIDS-infected persons have had sexual contact. Additionally, the Act provides for mandatory testing of certain groups, prohibits discrimination against individuals testing positive and regulates when life and health insurance companies may require HIV testing.

A Review of the Act

HIV Test Offer Requirements. The Act requires

hospitals, physicians and other health care providers to offer HIV testing to persons within several statutorily defined categories and to provide counseling for those individuals tested. The costs associated with testing and counseling are to be borne, to a certain extent, by the Rhode Island Department of Health (the Department).

The categories of persons that must be offered HIV testing include hospital patients,¹ persons being treated for a suspected sexually transmitted disease,² persons seeking prenatal care or family planning services,³ persons being treated at a facility for intravenous drug abusers,⁴ and persons submitting to a laboratory blood test for the purpose of obtaining a marriage license.⁵ When a person within any of these categories presents him/herself to a health care provider, the provider must give him/her an "AIDS Testing and Notification Form" (the Form), which the individual must sign and date in acknowledgment of the HIV testing offer.

The Form is to be developed by the Department and must state the following:

- (i) the public health rationale for HIV testing,
- (ii) the availability and cost of HIV testing and counseling,
- (iii) that test results are confidential with certain exceptions,
- (iv) a list of exceptions to confidentiality of test results,
- (v) that the test is voluntary and that an informed consent form must be signed before testing, and
- (vi) that by signing the Form the person acknowledges only that the HIV test and counseling have been offered.⁶

Any person accepting the testing offer may obtain both pretest and post-test counseling. The

The authors are attorneys at the law offices of Edwards & Angell in Providence, Rhode Island. They wish to acknowledge the generous editorial contribution made by Susan U. Fine, JD, MPH, Associate Vice President of Health Policy and Legal Affairs of the Hospital Association of Rhode Island.

Department is responsible for drafting regulations which, in accordance with acceptable medical standards, define the nature and scope of such counseling.⁷ (Based upon Department comment, these regulations should be available by late fall of 1988.) As indicated above, the Department is obligated to reimburse providers for the costs of counseling. The Department's obligation, however, differs among the categories of persons subject to the HIV testing offer.

The Act requires that the Department provide or pay for all counseling of hospital patients who receive an HIV test. If the Department chooses to pay rather than to provide counseling, it will negotiate with hospitals concerning their "incremental costs" of counseling and provide "reasonable reimbursement" of such costs.⁸ The Department will pay the reasonable costs of counseling for persons being treated for a suspected sexually transmitted disease,⁹ persons seeking prenatal care or family planning services,¹⁰ and persons being treated at intravenous drug abuse facilities,¹¹ after such costs are negotiated and committed to contract. In the case of marriage license blood testing, the Department, rather than pay for counseling, will provide pretest and post-test educational materials and provide post-test counseling for those individuals testing positive.¹²

Health care providers conducting testing pursuant to these HIV testing offer provisions must maintain the tested individuals' identities only at the site where the blood sample is drawn.¹³ Providers may not release the individuals' identities unless reporting test results to the Department (according to yet unissued regulations) or unless otherwise permitted by law.¹⁴ The Act's provisions concerning confidentiality and disclosure of HIV test results are discussed in greater detail below.

Informed Consent Requirements and Exceptions. All persons voluntarily tested for AIDS, whether pursuant to the HIV testing offer discussed above or on their own initiative, must read and sign an informed consent form before the provider conducts the test.¹⁵ The consent is invalid unless the individual discusses the test's implications with a "qualified professional," a term not defined in the Act. The consent form must include at least the following:

- (i) the name and signature of the party (parties) seeking and consenting to the HIV test,
- (ii) the name and nature of the test,
- (iii) the reason for conducting the test,
- (iv) the fact that the test results shall remain

confidential except as required by law, and

(v) an explanation of how test results will affect the tested person's ability to obtain services from the party requesting the test or from those for whom the party is acting.¹⁶

In certain situations persons may be tested for AIDS without granting or after refusing to grant their informed consent.¹⁷ A physician may perform an HIV test without an individual's consent when the individual is under one (1) year of age,¹⁸ is between the ages of one (1) and thirteen (13) and is displaying symptoms associated with AIDS,¹⁹ or is a minor under the guardianship of the Rhode Island Department for Children and Their Families and the Department director certifies that an HIV test is necessary to secure health or human services for that minor.²⁰ In addition, providers need not obtain informed consent for HIV testing in an emergency when it is impossible to obtain consent from either the patient or from the patient's guardian.²¹

Informed consent also is not required when the "occupation exception" is invoked.²² This exception permits testing an individual who has exposed a person (the complainant) to his/her blood or other bodily fluids during the performance of the complainant's occupation, if the complainant

(i) identifies the time, place, and nature of the exposure, and the parties and witnesses thereto within forty-eight (48) hours of the exposure,

(ii) submits within seventy-two (72) hours of the exposure to an HIV test and that test is negative, and

(iii) has suffered an exposure (i.e., needlestick, bite, splash over broken skin) to the blood or bodily fluids of the person to be tested in concentration sufficient to permit transmission of the AIDS virus.²³

Health care administrators must recognize that before their facilities test an individual for AIDS pursuant to the informed consent exceptions, including the health care worker exception discussed below, the facilities must make a reasonable effort to obtain the affected person's voluntary informed consent.²⁴ Furthermore, for their facilities' protection, administrators should maintain a well-documented record of their efforts to obtain consent.

Health Care Worker Exception. One of the more innovative provisions of the Act is the informed consent exception which allows health care workers to ascertain whether patient contact has increased their risk of contracting the AIDS virus.²⁵ The Act allows licensed health care facilities to

test a patient without consent if a health care worker at that facility sustains a "significant exposure" to the blood or bodily fluids of the patient and if that patient's blood has been drawn and is available.²⁶ If a sample of the patient's blood is not available and the patient refuses to consent, the health care worker may petition the Superior Court for an order to test the patient.²⁷ Before a blood sample or a patient may be tested, the affected health care worker must submit to an HIV test within seventy-two (72) hours of his/her exposure.²⁸

The Act creates an "exposure evaluation group" process to determine when a health care worker suffers a significant exposure. These groups are to consist of three (3) impartial health care professionals. In licensed health care facilities providing inpatient services, the group shall include the patient's attending physician, the chief of service, and a staff nurse.²⁹ For non-inpatient services in these facilities, the nurse shall be replaced by a representative from the employee health office.³⁰ In private physicians' offices, the exposure-evaluation group shall consist of three (3) physicians.³¹

Any person who performs an HIV test under the authorization of an exposure evaluation group shall not be liable for his/her actions unless that person acts in bad faith. Additionally, any member of the exposure evaluation group who in good faith determines that a health care worker has sustained a significant exposure and, in turn, authorizes the patient's HIV test, shall not be liable for his/her actions.³²

Mandatory HIV Testing. Under the Act, persons committed to an adult correctional institution after conviction for any criminal offense,³³ persons convicted of prostitution or lewdness,³⁴ and persons convicted of possession of any hypodermic instrument associated with intravenous drug abuse,³⁵ must undergo HIV testing. Consent is not required for such testing. Persons subject to mandatory testing shall receive pretest and post-test counseling. The Department will bear all costs associated with performing and reporting the results of the test, and with providing the counseling.³⁶

The Department of Corrections will not be permitted to punish or to deny recreational privileges to inmates solely because of a positive HIV test. The Department of Corrections, however, is responsible for preventing AIDS-infected inmates from infecting other inmates and the correctional staff. The Department of Corrections also is instructed to implement a comprehensive

AIDS education and drug treatment program for the inmates and staff at all correctional facilities in the state.³⁷

Confidentiality and Disclosure of HIV Test Results. All HIV test results are confidential and may not be disclosed by the testing facility or the provider without the prior written consent of the individual tested.³⁸ This strictly stated rule, however, is subject to numerous exceptions.

Consent to release HIV test results is not required when licensed health care facilities or laboratories report test results to the Department or to physicians and other "authorized medical personnel" who request that the test be performed.³⁹ Nor is a release necessary for a physician to enter HIV test results in a patient's medical record⁴⁰ or to notify other health professionals directly involved in the care of an individual who tests positive.⁴¹

A physician does not need a release to notify any person exposed to the blood or bodily fluids of an HIV positive individual who was tested voluntarily while a hospital patient or pursuant to certain of the informed consent exceptions, including the health care worker exception.⁴² Consent to release also is not required for a physician to notify any third party who has had close and continuous contact with an AIDS-infected patient. The physician, however, must be of the opinion that there is a clear and present danger of transmission of the AIDS virus to the third party and must believe that the AIDS-infected patient, despite the physician's strong encouragement, will not warn the third party.⁴³

The Act permits release of HIV test results in accordance with the confidentiality exceptions in the Rhode Island Mental Health Law and with most of the confidentiality exceptions in the state Confidentiality of Health Care Information Act (the Confidentiality Act).⁴⁴ Certain Confidentiality Act exceptions, however, are not applicable to HIV test results. Specifically, health care providers may not release HIV test results without consent to persons conducting scientific research or management audits, to law enforcement personnel, to the state cancer registry, or to a facility's malpractice insurance carrier or lawyer when the facility anticipates a medical liability action.⁴⁵

Test results may be released to comply with the Rhode Island Reports of Disease and Disability Act requiring that a written notice accompany an individual's body to embalmers or funeral directors if the individual had an infectious or contagious disease.⁴⁶ Likewise, to comply with

the state Notification After Exposure To Infectious Diseases Act, health care facilities may release HIV test results to the employer of any police officer, fire fighter or emergency medical technician when a patient treated or transported by one of the employer's personnel was diagnosed as having an infectious disease.⁴⁷

As is evident, the Act includes many provisions allowing the release of HIV test results without the tested individual's consent. The Act, however, imposes upon parties maintaining HIV test result information a burdensome notice requirement whenever they release such information.⁴⁸ Before disclosing an individual's HIV test results, the disclosing party must make a reasonable effort to inform the individual of the nature and the purpose of the disclosure, the disclosure date, and the recipient of the information. This notice requirement is waived only under the following circumstances:

- (i) when health care facilities report results to the Department, the Department for Children and Their Families, physicians, or other authorized medical personnel,
- (ii) when physicians enter results in a patient's record or notify other providers involved in the patient's treatment
- (iii) when providers include an infectious disease notice to embalmers and funeral directors, and
- (iv) when providers notify employers of police officers, fire fighters, or emergency medical technicians.⁴⁹

All entities maintaining HIV test records must keep the records (including those electronically stored) secure at all times, establish and enforce rules limiting access to the records, and train personnel who handle the records in security objectives and techniques.⁵⁰ Any violation by a health care facility or physician of the Act's confidentiality, record-keeping, or third-party notification requirements may result in civil and criminal penalties as provided in the Confidentiality Act.⁵¹

Discrimination Prohibited Against Individuals With AIDS. In one of its more sweeping provisions, the Act prohibits discrimination against HIV-positive individuals in housing, employment, granting of credit, public accommodations, and delivery of services (including medical services).⁵² Employers may not require HIV test results as a condition of employment unless the employer demonstrates that there is a clear and present danger that the recruit will transmit the AIDS virus to others. Any individual who believes that he/she has been the victim of unlawful discrim-

ination because of a positive HIV test may bring an action for relief before the Rhode Island Human Rights Commission.⁵³

Life Insurance Exemption. Companies offering life insurance policies in Rhode Island are exempt from the Act and may require individuals to be tested for AIDS in order to determine insurability.⁵⁴ Life insurance companies must give individuals prior written notice of any AIDS testing requirement and may only conduct the test if given written authorization by the individual. It is important to note that life insurance companies are neither permitted to cancel nor to refuse to renew a life insurance policy which has not lapsed solely because the insured individual has tested positive for the AIDS virus.⁵⁵

Health Benefits. A company offering or selling health benefits in Rhode Island may require an individual to be tested for AIDS when the individual is applying for coverage under an individual health benefit policy or a small group health insurance plan.⁵⁶ Likewise, testing may be required if an individual seeks coverage under a plan in which he/she chose not to enroll when first eligible.⁵⁷ Like life insurance companies, health insurers in Rhode Island are neither permitted to cancel nor to refuse renewal of a health benefit policy because an individual tests positive for AIDS.⁵⁸

The Act establishes a commission to develop a risk pool plan in which all health insurers are to participate and share proportionately the risk and cost of insuring AIDS patients.⁵⁹ The commission, an eleven-member panel representing various interested parties, must present its risk pool plan report to the General Assembly on or before February 1, 1989.

An Analysis of the Act

Hospital Considerations. To prepare for the Act's implementation on January 1, 1989, hospital administrators will be obliged to establish a variety of new protocols. Hospitals should consider amending their admissions procedures to include use of the AIDS Testing and Notification Form and an informed consent protocol specific to HIV testing. Hospitals may be obliged to draft policies on pretest and post-test counseling and on the Act's many confidentiality and disclosure requirements. In addition, hospitals may want to adopt policies that permit their employees to take advantage of the Act's health care worker exception.

Hospitals must offer an HIV test and make available the AIDS Testing and Notification Form

to all patients, unless the patient's physician determines that the test offer is inappropriate (and states so in the patient's record) or the patient is excluded from the offer requirement under the Department's regulations. (While these regulations have not yet been issued, the Department has indicated informally that older persons will be excluded from the test offer requirement.) After hospitals identify which patients must receive the Form, they must ensure that each of these patients reads, signs, and dates the Form. Hospital administrators should note that the Act does not distinguish between inpatients and outpatients. The HIV test must be offered and the Form made available to both.

Hospitals must obtain the informed consent of any patient choosing to be tested. The Act does not require the Department to draft these forms as it does with the AIDS Testing and Notification Form. Hospitals may devise their own consent forms as long as they include the five (5) elements⁶⁰ listed in the Act. For the consent to be valid, the individual must discuss the HIV test's implications with a qualified professional before signing the form. "Qualified professional" is not defined in the Act. Its interpretation, presumably, is left to the various health care providers.

The Act does not provide for any specific penalty if a hospital fails properly to offer the HIV test or fails properly to obtain informed consent. A hospital's license is put at risk, however, if the hospital does not comply with the requirements of the Rhode Island Health Care Facility Licensing Act. The HIV testing offer and informed consent provisions are incorporated in the licensing act.

All patients tested under the Act's testing offer provisions must receive pretest and post-test counseling.⁶¹ The Act states that the Department will either provide or pay for all counseling. It requires the Department to negotiate with hospitals concerning counseling costs and provide reasonable reimbursement. Until the Department issues its regulations on the nature and scope of the counseling required, hospital administrators may find it difficult to prepare for their counseling responsibilities.

Hospitals must contend with new requirements on maintaining the confidentiality of HIV test results. While the Act incorporates most of the exceptions to the rule against release of patient information in the Confidentiality Act, certain of those exceptions, as discussed above, do not apply to HIV test information. Applying the

state's confidentiality rules to HIV test results differently from the way they are applied to all other health care information poses a difficult problem for hospitals. Although the Act's purported function is to discourage the stigmatization of persons who test HIV positive, the legislature is requiring hospitals to treat medical records with HIV test result information different from all others.

The Act's confidentiality provisions present other problems. The provisions focus only on maintaining the confidentiality of test results; other AIDS related information is not addressed in the Act. Theoretically, if a facility takes special precautions to keep HIV test results confidential, but does little to maintain the confidentiality of treatment related to AIDS — such as a patient's response to zidovudine (AZT) — the facility would be in compliance with the Act.⁶²

As noted, the disclosure provisions require providers to make a reasonable effort to inform individuals in advance that their HIV test results will be released. For instance, if a health insurer requests a hospital to release to it a patient's HIV test results for the purpose of adjudicating a health insurance claim (which the hospital may do without the patient's consent pursuant to the state Confidentiality Act), the hospital must attempt to find the patient, even after he/she is discharged, before disclosing the patient's test results. If the hospital does not notify the individual or does not demonstrate that "reasonable efforts" were used, the hospital may expose itself to liability.

Hospitals must keep records of HIV test results secure at all times and are obligated under the Act to train their personnel specifically in regard to the security of these records. For many hospitals, these record-keeping provisions may be stricter than those currently in place. Hospitals may wish to evaluate their current procedures to determine whether they satisfy the Act's requirements.

The health care worker exception may be the Act's most important provision for hospitals and other health care providers. When health care employees suspect that they have been exposed to the AIDS virus from contact with a patient's blood or bodily fluids, they can avail themselves of the testing provisions. The facility must make a reasonable effort to obtain the patient's voluntary informed consent. If consent is refused, the health care worker must submit to a baseline AIDS test within seventy-two (72) hours of the exposure. If the baseline test is negative and a

sample of the patient's blood is available, the sample may be tested immediately. (This is, in essence, much of the relief health care employees have sought.) If a blood sample is not available, the health care worker may seek a court order compelling performance of the HIV test.

To facilitate the health care worker exception process, hospitals should consider preparing their physician and nursing staffs to participate as members of exposure evaluation groups. Hospitals also will want to ensure that their liability coverage will protect individuals' participation in these groups.

The groups will have to determine clinically whether an employee's exposure constitutes a "significant" exposure.⁶³ Because of their composition, evaluation groups in the hospital setting — consisting of the attending physician, the chief of service and a staff nurse — may have different membership with each incident. Hospitals will want to develop procedures for their evaluation groups to impose some conformity on exposure determinations.

Physician Considerations. Physicians will be involved closely with much of the HIV testing conducted pursuant to the Act. Physicians, in their own offices, must follow the same HIV testing offer and informed consent procedures as hospitals when the physician's patients require treatment for a sexually transmitted disease, request prenatal care or family planning services, or request a blood test for a marriage license application. More problematic, each patient who accepts the testing offer must be provided pretest and post-test counseling. The Act requires the Department to issue regulations regarding counseling, but it is not clear whether physicians will have to provide counseling to their private patients themselves or whether they may refer patients elsewhere.

For each patient who volunteers to be tested for AIDS, whether pursuant to the HIV testing offer or otherwise, physicians must obtain the patient's written informed consent in a manner consistent with the Act. Physicians should be sensitive to the various exceptions to the informed consent requirement. In particular, a physician may be called upon to test a person under the occupation exception. This provision allows any individual allegedly exposed to the AIDS virus during performance of his/her occupation to require the testing of the person responsible for the exposure. Although the occupation exception describes a process for the complainant to

document the exposure, it neither provides for any oversight of this process nor states who should decide whether the exposure was significant enough to justify testing the individual whose blood or bodily fluids are at issue. It is likely that part of the burden for making these decisions will fall to physicians.

Physicians should be aware of the health care worker exception to the informed consent requirement. This exception, described under the Hospital Considerations section above, applies to all private physicians' employees. The process that a physician's employees follow if exposed to the blood or bodily fluids of a patient is the same as that followed by hospital employees. In private physicians' offices, however, the team deciding whether an exposure is significant is composed of three (3) physicians. Physicians will be obliged to prepare not only for the initiation of this testing process by their employees, but also for their own involvement in HIV exposure evaluations.

The Act clarifies physicians' responsibilities regarding the confidentiality and disclosure of HIV test results. Physicians may enter test results in a patient's medical record, but they must do so as they would for any other diagnostic test. Physicians may notify other health professionals directly involved in the care of the individual who tested positive for AIDS. Significantly, physicians may disclose positive test results to third parties with whom an AIDS-infected patient is in close and continuous contact if the nature of the contact, in the physician's opinion, poses a clear and present danger of AIDS transmission to that third party and if the physician has reason to believe that the patient will not warn the third party despite the physician's strong encouragement. The Department director is charged with establishing a procedure by which physicians will contact third parties.

As discussed in the Confidentiality and Disclosure section, HIV test results may be released by a physician without a patient's consent under most circumstances listed in the Confidentiality Act. If a physician questions whether he/she may release test results, the physician should contact counsel. The physician also should determine whether he/she needs to notify the tested individual of the disclosure before releasing the test result information.

Physicians are held to the same standard as hospitals for maintaining the confidentiality of HIV test results. Physicians must establish and enforce rules limiting access to these records and

must train their personnel in security objectives and techniques. Breach of any of the confidentiality or disclosure provisions may result in civil or criminal penalties, as discussed above.

Conclusion

The Act is comprehensive and complex. Only after the state's health care providers begin its implementation will all of the Act's operational implications become apparent. Although the Department has an opportunity under certain portions of the Act to explicate unclear provisions, its regulatory authority is limited. Indeed, health care providers will find that implementing the Act will prove to be a continuous challenge.

Notes

- ¹ *R.I. Gen. Laws* §23-17-31 (1988). Hospitals do not have to offer HIV testing to a patient if the test is deemed inappropriate by the patient's physician and if such a determination is indicated in the patient's record. Nor must hospitals offer HIV testing to those patients excluded from testing by regulations of the Rhode Island Department of Health. Regulations regarding exclusion are not yet promulgated.
- ² *Id.* at §23-11-17.
- ³ *Id.* at §23-13-19.
- ⁴ *Id.* at §40.1-24-20.
- ⁵ *Id.* at §15-2-3.
- ⁶ *Id.* at §23-6-11(7).
- ⁷ See *id.* at §§23-17-31, 23-11-17, 23-13-19, 40.1-24-20 and 15-2-3.
- ⁸ *Id.* at §23-17-31.
- ⁹ *Id.* at §23-11-17.
- ¹⁰ *Id.* at §23-13-19.
- ¹¹ *Id.* at §40.1-24-20.
- ¹² *Id.* at §15-2-3.
- ¹³ See *id.* at §§23-17-31, 23-11-17, 23-13-19, 40.1-24-20 and 15-2-3.
- ¹⁴ See *id.* at §§23-17-31, 23-11-17, 23-13-19, 40.1-24-20 and 15-2-3.
- ¹⁵ *Id.* at §23-6-12. A person subject to the HIV testing offer requirements must first sign the "AIDS Testing and Notification Form" indicating that the test was offered and then sign an informed consent form granting his/her approval to have the test conducted.
- ¹⁶ *Id.* at §23-6-13.
- ¹⁷ *Id.* at §23-6-14. The language in this section of the Act is particularly troublesome. It states that a physician "may secure a test" if one of the enumerated informed consent exceptions applies. This language, read strictly, means only that informed consent is not necessary to *test* an individual's blood for the AIDS virus. It does not address whether informed consent is necessary to puncture one's skin and *draw* blood. Accordingly, if an individual refuses to grant his/her consent to have his/her blood drawn and tested, and the party requesting the test properly invokes one of the informed consent exceptions to proceed with testing, that party is protected under the Act for testing the blood, but may be guilty of battery for coming into contact with the individual when the blood is drawn.
- ¹⁸ *Id.* at §23-6-14(a).
- ¹⁹ *Id.* at §23-6-14(b).
- ²⁰ *Id.* at §23-6-14(c).
- ²¹ *Id.* at §23-6-14(f).
- ²² *Id.* at §23-6-14(d).
- ²³ *Id.*
- ²⁴ *Id.* at §26-6-15.
- ²⁵ *Id.* at §23-6-14e.
- ²⁶ *Id.*
- ²⁷ *Id.* at §23-6-14(e)(i).
- ²⁸ *Id.* at §23-6-14(e)(ii).
- ²⁹ *Id.* at §23-6-11(6)(i).
- ³⁰ *Id.*
- ³¹ *Id.* at §23-6-11(6)(ii).
- ³² *Id.* at §23-6-14(e)(iii)
- ³³ *Id.* at §42-56-37.
- ³⁴ *Id.* at §11-34-10.
- ³⁵ *Id.* at §21-28-4.18.
- ³⁶ See *id.* at §§42-56-37, 11-34-10 and 21-28-4.18.
- ³⁷ *Id.* at §42-56-37.
- ³⁸ *Id.* at §23-6-17.
- ³⁹ *Id.* at §23-6-17(a).
- ⁴⁰ *Id.* at §23-6-17(b)(i).
- ⁴¹ *Id.* at §23-6-17(b)(ii).
- ⁴² *Id.* at §23-6-17(b)(iii).
- ⁴³ *Id.* at §23-6-17(b)(v).
- ⁴⁴ *Id.* at §23-6-17(c).
- ⁴⁵ See *id.* at §23-6-17(c). Hospitals, however, may disclose HIV test results without a patient's consent to a court, lawyer or medical liability insurance carrier if the patient actually brings a medical liability action against a health care provider. *Id.* §5-37.3-4(b)(8).
- ⁴⁶ *Id.* at §23-6-17(d); see *id.* at §23-5-9.
- ⁴⁷ *Id.* at §23-6-17(d); see *id.* at §23-28-6-2.
- ⁴⁸ *Id.* at §23-6-20.
- ⁴⁹ *Id.*
- ⁵⁰ *Id.* at §23-6-18.
- ⁵¹ *Id.* at §23-6-19. Civil penalties under the Confidentiality Act include payment of actual and exemplary damages. Anyone who intentionally and knowingly violates the confidentiality provisions shall be subject, upon conviction, to criminal penalties of up to a \$1000 fine and/or imprisonment for not more than six (6) months. *Id.* at §5-37.3-9.
- ⁵² *Id.* at §23-6-22.
- ⁵³ *Id.*
- ⁵⁴ *Id.* at §23-6-24(a).
- ⁵⁵ *Id.*
- ⁵⁶ *Id.* at §23-6-24(b). A small group health insurance plan is defined in the Act as a group having fewer than twenty-five (25) employees eligible to participate in an employer-sponsored plan or, in the case of non-employer groups, a group with fewer than twenty-five (25) employees. *Id.* §23-6-24(b)(ii).
- ⁵⁷ *Id.* at §23-6-24(b)(iii).
- ⁵⁸ *Id.* at §23-6-24(b).
- ⁵⁹ *Id.* at §23-6-24(c).
- ⁶⁰ See *supra* pp. 438.
- ⁶¹ When patients are tested pursuant to the health care worker exception or any of the other enumerated exceptions to the informed consent requirement, see *supra*, pp. 438, pretest and post-test counseling are not mandated as in the testing offer and mandatory testing sections of the Act. Despite this inconsistency, hospitals should consider providing counseling for all HIV testing.
- ⁶² It must be noted that in such a scenario, if information concerning a patient's response to AZT was improperly released, the disclosing party would likely be violating the state Confidentiality Act.
- ⁶³ While the Act includes a definition of "significant exposure" in the provision regarding persons potentially exposed to the AIDS virus during the performance of their occupation, see *R.I. Gen. Laws* §23-6-14(d)(iii), and *supra*, notes 22-23 and accompanying text, it does not provide a definition in the health care worker exception. The determination of whether a significant exposure has occurred in the health facility setting is left to the exposure evaluation team. However, the definition of "significant exposure" provided in the occupation exception may provide the evaluation teams with some parameters for their decisions.

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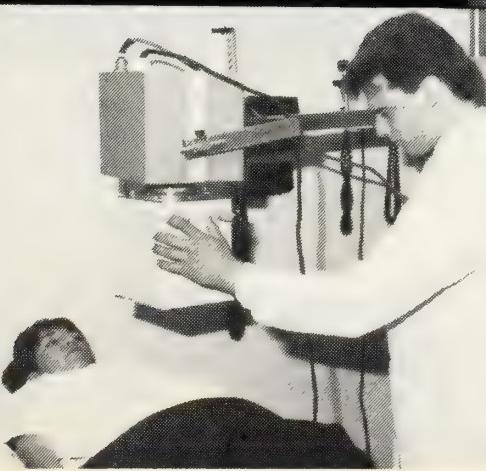
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PERIPATETICS

Governor Edward DiPrete has recently named **Dr David P. Carter** to serve on the Legislative Commission studying Medicare assignment. **Dr Carter** was also appointed by the Rhode Island Chapter of the American Academy of Family Physicians (AAFP) to be one of two delegates representing the chapter at the annual meeting of the AAFP in New Orleans in October.

• • •

The Boston University Hospital Surgical Residency Program recently honored **Dr Stephen J. Hoye**, Surgeon-in-Chief at Memorial Hospital of Rhode Island, as "Outstanding Surgical Teacher of the Year."

• • •

Newly appointed to the medical staff of South County Hospital are **Dr Robert C. Marchand**, orthopedic surgeon and **Dr John V. Chobanian**, gastroenterologist.

• • •

Dr Carl Feinstein has been appointed to the position of clinical director at Bradley Hospital. **Dr Feinstein**, associate professor of psychiatry in the Brown University Program in Medicine, was previously director of the Developmental Disabilities Program and also served as president of the medical staff at Bradley Hospital.

• • •

A specialist in gynecologic and pelvic surgery, **Dr Giglia A. Parker** has been appointed Associate Director of Gynecologic Surgery in the Department of Obstetrics and Gynecology at Women & Infants Hospital. She is also Assistant Professor of Obstetrics and Gynecology for the Brown University Program in Medicine.

• • •

Dr Edward A. Iannuccilli, a gastroenterologist and Director of Medical Education at Rhode Island Hospital, is the first Clinical Professor to be appointed in the Department of Medicine at Brown University.

• • •

The American College of Radiology named **Dr Peter D. T. Clarisse** as a fellow during ceremonies at the recent annual meeting held in Cincinnati, Ohio.

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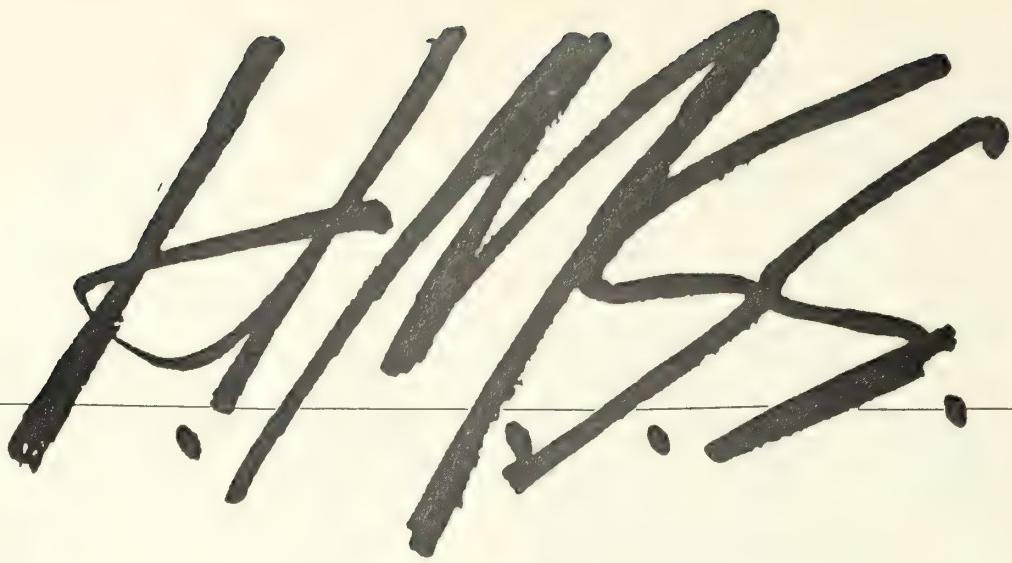
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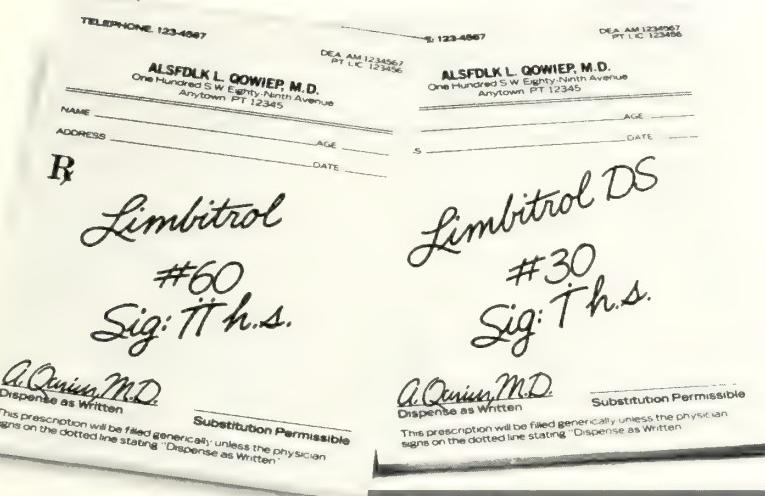
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Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

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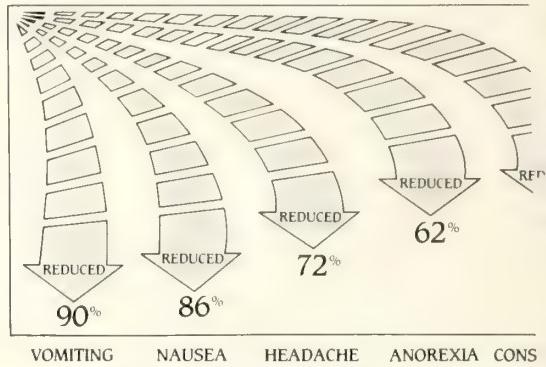
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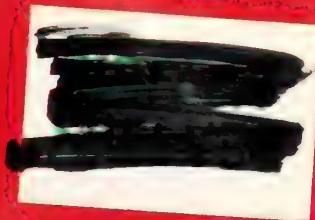
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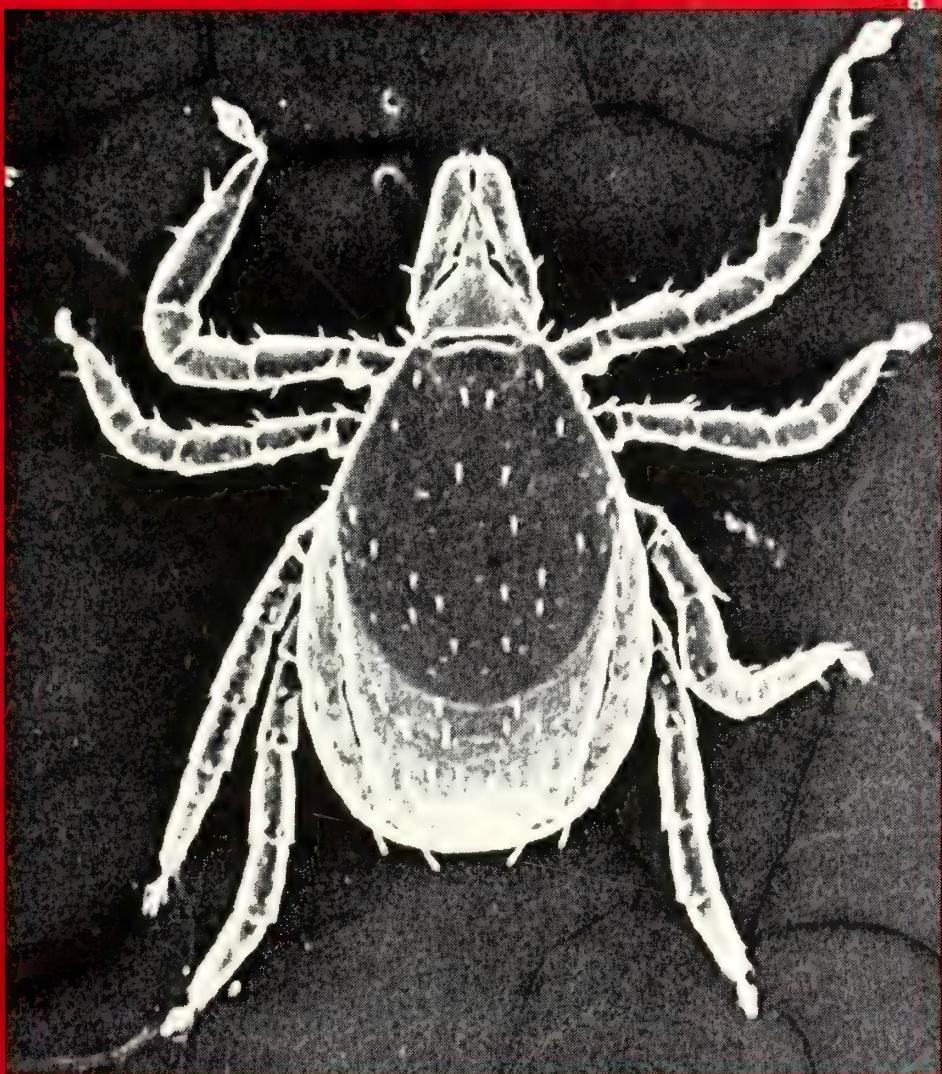


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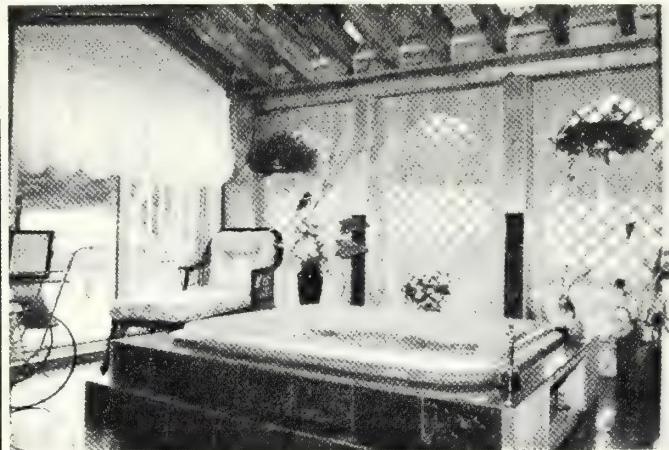
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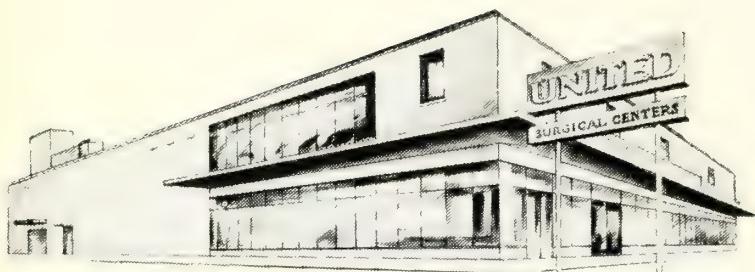
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Gastrointestinal Tract and AIDS

Cover: *Ixodes dammini, female deer tick. Photo courtesy of Kerwin E. Hyland, PhD. The Lyme disease-causing agent, B burgdorferi, has been found in the digestive tract of I dammini. See page 477.*

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*Happy Holidays
to
You and Yours*

EDITORIAL

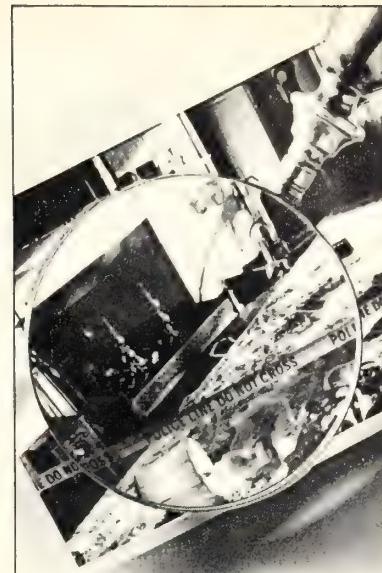
Watch Out For Lyme Disease

We have devoted this issue of the *Journal* to Lyme borreliosis because of its special interest to Rhode Islanders. The disorder was first identified locally in Lyme, Connecticut, which is hardly more than an hour's drive from Providence. The reviews have been prepared at our request by experts in the Rhode Island Department of Health and the University of Rhode Island. We are close to the epicenter of the disease, which has been identified along the Atlantic Coast from New Hampshire to Maryland, especially in Massachusetts, Rhode Island, Connecticut, and New York. Large numbers of the carrier tick *Ixodes dammini* are found on Block Island, Prudence Island, and Washington County (the old "South County"). The Massachusetts islands and Cape Cod are also endemic areas. In all of these locations the white-tailed deer and the white-footed mouse, the favored hosts, are widely prevalent.

Rhode Island harbors a significant amount of the disease with 163 cases reported between 1982 and 1987. The Health Department believes that this certainly does not reflect the actual incidence in the state. A Rhode Island physician who summers on Cape Cod is known to have contracted the disease.

Because of the profound incidence in Rhode Island we have deemed it worthwhile to alert the physicians of the state to its significance, so that they may be mindful of it when confronted with cases of obscure fever, arthritis, skin disorders, or, in fact, a myriad of other signs and symptoms.

Seebert J. Goldowsky, MD



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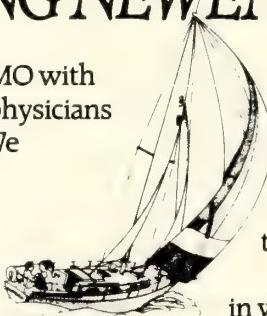
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EDITOR'S MAILBOX



Major Drug Related Inducer of Illness in the US Overlooked

To the Editor:

During the summer you reported drug related causes for emergency room visits in Rhode Island. I believe that the reports missed the major drug related inducer of illness in the United States. That drug of course is legal. It comes in packages that can be purchased conveniently at most stores and at many vending machines. It is pushed by some of the largest corporations in the United States. It is defended by some of the most powerful Senators and Presidents of the United States. I don't understand why physicians in Rhode Island would ignore it, although I do understand why the Health Department would ignore it. They too are afraid of the rich and powerful.

In 1987, State Representative Nicholas Tsiongas, MD, submitted legislation which would have forced tobacco companies to pay for tobacco related illnesses that occurred in the state of Rhode Island. While the bill was opposed by ex-governor Dennis Roberts, Jr, lobbyist for the tobacco industry, it was not supported by Denman Scott, MD, or his department.

Forcing the tobacco companies to pay for the illnesses their products produce is not only equitable, but will serve to raise the price of the product. Just as with asbestos (which is legal but almost unused), this will eventually lead to its voluntary removal from the market.

David Egilman, MD, MPH
Clinical Instructor in Community Health
Brown University

Re: Board of Medical Licensure and Discipline

To the Editor:

I am writing this letter with hopes that it would be included in the monthly issue of the *Rhode Island Medical Journal*.

Most of us understand the need to have the new Board of Medical Licensure and Discipline and commend the job they are doing in an effort to ensure quality control throughout the medical community.

It is unfortunate, however, that when a physician makes a mistake and this is brought to the Board for review, his name winds up in the *Providence Journal* for publication to the lay community. Currently there is a statute which makes this public information. While I realize that attorneys do not make mistakes and insurance companies do not make mistakes, physicians are human and occasionally the most conscientious of physicians will make an error. A conscientious physician is his own worst critic and will do his utmost not to repeat this mistake; and, if he must be censored by the Board of Medical Licensure and Discipline, so be it. It is a terrible thing, however, to see this physician's name appear in the newspaper for public castigation. Have we returned to the days when Hester had to wear an "A" around her neck as a sign of her mistake? Perhaps we should reinstitute the ducking stools that were prevalent in the witchcraft trials in Salem.

It is unfortunate that a profession that is trying so hard to police itself has to go to the extreme of issuing hair shirts to its members instead of dealing with these problems in private. No purpose is served in ruining a physician's career by

public disclosure in the *Providence Journal* so that he can be held up to ridicule unless the problem is severe enough that the doctor has lost his medical license and the public needs to know that physician is no longer allowed to practice.

Howard Sturim, MD, FACS

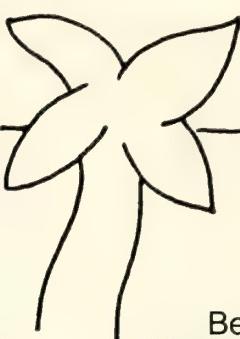
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INDICATIONS AND USAGE

Cipro[®] is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Lower Respiratory Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Streptococcus pneumoniae*.

Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (penicillinase and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, and *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, and *Pseudomonas aeruginosa*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, and *Streptococcus faecalis*.

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella flexneri*,^a and *Shigella sonnei*^a when antibacterial therapy is indicated.

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with Cipro[®] may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

CIPROFLOXACIN SHOULD NOT BE USED IN CHILDREN, ADOLESCENTS, OR PREGNANT WOMEN. The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related drugs such as nalidixic acid, cinoxacin, and norfloxacin also produced erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species (SEE ANIMAL PHARMACOLOGY SECTION IN FULL PRESCRIBING INFORMATION).

PRECAUTIONS

General: As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation, which may lead to tremor, restlessness, lightheadedness, confusion, and very rarely to hallucinations or convulsive seizures. Therefore, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral arteriosclerosis or epilepsy, or other factors which predispose to seizures (SEE ADVERSE REACTIONS).

Quinolones may also cause anaphylactic reactions and cardiovascular collapse. Anaphylactic reactions may require epinephrine and other emergency measures.

Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals. Crystalluria related to ciprofloxacin has been reported only rarely in man, because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated, and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded. Alteration of the dosage regimen is necessary for patients with impairment of renal function (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

Drug Interactions: Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored and dosage adjustments made as appropriate.

Antacids containing magnesium hydroxide or aluminum hydroxide may interfere with the absorption of ciprofloxacin, resulting in serum and urine levels lower than desired, concurrent administration of these agents with ciprofloxacin should be avoided.

Probenecid interferes with the renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

As with other broad-spectrum antibiotics, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition and microbial susceptibility testing is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients: Patients should be advised that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should also be advised to drink fluids liberally and not take antacids containing magnesium or aluminum concomitantly or within two hours after dosing. Ciprofloxacin may cause dizziness or lightheadedness; therefore patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below.

Salmonella/Microsome Test (Negative)

E. coli DNA Repair Assay (Negative)

Mouse Lymphoma Cell Forward Mutation Assay (Positive)

Chinese Hamster V₇₉ Cell HGprt Test (Negative)

Syrian Hamster Embryo Cell Transformation Assay (Negative)

Saccharomyces cerevisiae Point Mutation Assay (Negative)

Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)

Rat Hepatocyte DNA Repair Assay (Positive)

Thus, two of the eight tests were positive, but the following three *in vivo* test systems gave negative results.

Rat Hepatocyte DNA Repair Assay

Micronucleus Test (Mice)

Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in animals have not yet been completed.

Pregnancy - Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. SINCE CIPROFLOXACIN, LIKE OTHER DRUGS IN ITS CLASS, CAUSES ARTHROPATHY IN IMMATURE ANIMALS, IT SHOULD NOT BE USED IN PREGNANT WOMEN (SEE WARNINGS).

CONVENIENT B.I.D. DOSAGE

Recommended dosage schedule

Severity of Infection Site*	Severity of Infection	Dosage
Respiratory Tract*	Mild/Moderate	500 mg q12h
Bone and Joint*	Severe/Complicated	750 mg q12h
Skin/Skin Structure*	Severe/Complicated	500 mg q12h
Urinary Tract*	Mild/Moderate	250 mg q12h
	Severe/Complicated	500 mg q12h
Infectious Diarrhea*	Mild/Moderate/Severe	500 mg q12h

Nursing Mothers: It is not known whether ciprofloxacin is excreted in human milk; however, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. Because of this, and because of the potential for serious adverse reactions from ciprofloxacin in nursing infants, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Ciprofloxacin should not be used in children because it causes arthropathy in immature animals (SEE WARNINGS).

ADVERSE REACTIONS

Ciprofloxacin is generally well tolerated. During clinical investigation, 2,799 patients received 2,868 courses of the drug. Adverse events that were considered likely to be drug related occurred in 7.3% of courses, possibly related in 9.2%, and remotely related in 3.0%. Ciprofloxacin was discontinued because of an adverse event in 3.5% of courses, primarily involving the gastrointestinal system (1.5% skin (0.6%), and central nervous system (0.4%).

The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and rash (1.1%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below. Those typical of quinolones are italicized.

GASTROINTESTINAL (See above), painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding.

CENTRAL NERVOUS SYSTEM (See above), dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.

SKIN/HYPERSENSITIVITY (See above), pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctiva or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum.

Allergic reactions ranging from urticaria to anaphylactic reactions have been reported.

SPECIAL SENSES blurred vision, disturbed vision, change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, bad taste.

MUSCULOSKELETAL joint or back pain, joint stiffness, aches, neck or chest pain, flare-up of gout, gout, arthritis, arthralgia.

RENAL/URINARY interstitial nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis.

CARDIOVASCULAR palpitations, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.

RESPIRATORY epistaxis, laryngeal or pulmonary edema, hiccup, hemoptysis, dyspnea, bronchospasm, pulmonary embolism.

Most of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

In several instances, nausea, vomiting, tremor, restlessness, agitation, or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship.

Hepatic - Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).

Hematologic - eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%).

Renal - Elevations of Serum creatinine (1.1%), BUN (0.9%).

CRYSTALLURIA, CYLINDURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were: Elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leukocytosis.

OVERDOSAGE

Information on overdosage in humans is not available. In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment. Adequate hydration must be maintained. In the event of serious toxic reactions from overdosage, hemodialysis or peritoneal dialysis may aid in the removal of ciprofloxacin from the body, particularly if renal function is compromised.

DOSAGE AND ADMINISTRATION

The usual adult dosage for patients with urinary tract infections is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, 500 mg may be administered every 12 hours.

Respiratory tract infections, skin and skin structure infections, and bone and joint infections may be treated with 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

The recommended dosage for infectious diarrhea is 500 mg every 12 hours.

In patients with renal impairment, some modification of dosage is recommended (SEE DOSAGE AND ADMINISTRATION SECTION IN FULL PRESCRIBING INFORMATION).

HOW SUPPLIED

Cipro[®] (ciprofloxacin HCl/Miles) is available as tablets of 250 mg, 500 mg, and 750 mg in bottles of 50, and in Unit-Dose packages of 100 (SEE FULL PRESCRIBING INFORMATION FOR COMPLETE INFORMATION).

*Due to susceptible strains of indicated pathogens.
See indicated organisms in Prescribing Information.

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Lyme Disease

A Review

Erica E. Jost, MD
Marilyn A. Rittmann, RN
Barbara A. DeBuono, MD

Lyme disease, a borreliosis, is a newly recognised disease of people and animals resulting not infrequently in chronic sequelae and rarely in death. Moreover, since the Centers for Disease Control (CDC) began surveillance of Lyme Disease it is now recognised to be the most common, if not most serious, tick-borne zoonosis in the United States. Because the vector responsible for transmission of the disease from animals to human beings is distributed over a wide habitat, because several species of tick are capable of transmission, and because these ticks parasitise a variety of hosts, it is unlikely that an environmentally applied control measure will be effective in reducing significantly the incidence of the disease in human beings in the near future. Therefore, both a high index of suspicion and a working knowledge of current modes of diagnosis and therapy

are necessary to treat the infection and prevent sequelae. Furthermore, the most feasible measure of control of this disease in human beings is education of the public in methods of prevention of infection by avoidance and removal of the ticks.

History

Lyme disease, now known to be a multisystem disease of protean manifestations and first recognised as a clinical entity in 1975, was initially described by Afzelius in Sweden in 1909 as *erythema chronicum migrans*, a rash which occurred after a bite by the tick *Ixodes ricinus*.^{71, 81} It was described in Europe in association with arthritis and neurological signs and symptoms in the 1920s before it was recognised in North America, when the rash was first diagnosed in 1970.⁵⁷ In 1975 it was brought to medical attention by two mothers in Lyme, Connecticut, who were concerned by the geographical clustering since 1972 of an unusual illness in children in their town: an affliction characterised by recurrent attacks of asymmetric, pauciarticular arthritis, mostly of large joints, first thought to be a variant of juvenile rheumatoid arthritis.⁷³ In two of three towns along the Connecticut River from which cases were sampled, six families had more than one member ill with the new disease and on four country roads ten per cent of the children were sick. As physicians from the academic, private, and public sectors investigated these illnesses, a clinical pattern distinct from that

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of juvenile rheumatoid arthritis and other known arthritides emerged: a unique association of recurrent oligoarthritis (most frequently in the knee) with a characteristic antecedent discrete annular rash, erythema chronicum migrans. Epidemiologic data at the time was not consistent with juvenile rheumatoid arthritis (JRA) or acute rheumatic fever because the prevalence of this new illness was three times that expected for JRA in a community of that size, because there was geographical, seasonal, and familial clustering, and because 25 per cent of those with the arthritis reported an antecedent rash.⁷¹ The new clinical entity was named Lyme arthritis. Combined with the patient's history of a tick bite, the rash suggested a similarity with the erythema chronicum migrans of Europe, which had been reported only once in United States medical literature, in 1970.⁵⁷ An overall picture of what we now know to be the many manifestations of a single disease was not evident at that time: the European patients had been reported as isolated cases of what were thought to be different illnesses. In contrast, the American illness seemed to progress frequently to *multisystem* disease: rheumatic, neurologic, and cardiac abnormalities.⁷¹ Therefore, the name was changed from Lyme arthritis to Lyme disease.

In retrospect, the earliest case described in the United States was probably that of a patient on Cape Cod, Massachusetts in 1962; and the earliest case in Lyme was in 1965. It has since been reported from 35 states.

The Causative Organism

In 1981 Willy Burgdorfer isolated the causative agent of Lyme disease, a new microaerophilic spirochete (ultimately named *Borrelia burgdorferi*), from the midgut of an infected deer tick, *Ixodes dammini*, on Shelter Island, off Long Island, N.Y.^{11, 27} Ticks infected with *B. burgdorferi* were allowed to feed on rabbits which developed small skin lesions progressing to erythema chronicum migrans 10 to 12 weeks after tick engorgement. Not only were there high titres of antibody (by indirect immunofluorescence) to the spirochetes in the sera of exposed rabbits, but there were also high titres of equivalent antibodies in the sera of nine patients with clinically diagnosed Lyme disease.¹¹ In 1982 the organism was cultured from the blood, cerebrospinal fluid, and periphery of skin lesions in patients with Lyme disease.^{7, 68} Spirochetes in the European sheep tick, *I. ricinus*, were found to be similar to those in New World ixodid ticks: DNA from European

and North American isolates were 75 to 100 per cent homologous — suggesting almost identical causes of erythema chronicum migrans and its complications on both sides of the Atlantic Ocean.⁵³ *Borrelia burgdorferi* is the only spirochete known to be pathogenic to the human host from which lipopolysaccharide has been extracted; it is pyrogenic to animals, mitogenic for human mononuclear cells, and cytotoxic to macrophages, possibly a factor in the enhanced virulence of this spirochete.²⁸

The Vector

Prior to the identification of the aetiologic agent, the association of the disease with a species of tick, *Ixodes dammini*, was noted in Connecticut in 1977: of 314 patients examined in 1976-1982, 31 per cent recalled a tick bite at the site where erythema chronicum migrans subsequently appeared, and six patients saved the tick, identified as the nymphal stage of *I. dammini*.⁶³ The distribution of *I. dammini*, now recognised as the primary arthropod vector for Lyme disease in the United States, was correlated geographically with the Connecticut River in 1978: the white-footed or deer mouse *Peromyscus leucopus* (the preferred host of the larval, nymphal, and immature adult tick) was 12 times as likely to be tick-infested on the eastern bank as on the western bank, the white-tailed deer *Odocoileus virginianus* (the preferred host for the adult tick and the reservoir for overwintering) was 16 times as likely to be infested on the eastern bank, and the disease was 30 times as frequent on the eastern bank as on the western bank.⁷⁹

In the United States, the geographical distribution of Lyme disease in human beings is directly correlated to the geographic distribution of the tick *I. dammini* and other ixodid ticks. There are three endemic foci: (1) the northern Atlantic coast from New Hampshire to Maryland, especially Massachusetts, Rhode Island, Connecticut, and New York; (2) the northern Midwest, particularly northern Minnesota and Wisconsin; and (3) the Pacific Northwest, primarily northern California and Oregon, but also Utah and Nevada. *I. dammini* is native to New England and the Midwest; *I. pacificus* is the tick associated with Lyme Disease in the Pacific Northwest; and recently, it has been suggested that *I. scapularis* may be implicated in cases of Lyme disease in the Deep South.^{53, 63, 70} The interface between *I. dammini* and *I. scapularis* probably occurs in Virginia and Maryland.¹²

In Rhode Island, large numbers of *I. dammini*

can be found on Block Island, on Prudence Island, and in Washington County.

Borrelia burgdorferi has been isolated from all three ixodid species, although *I. dammini* remains the predominant vector of Lyme disease in the United States. There is no reason to believe that these species (except *I. scapularis*) do not transmit the disease in Canada: *I. dammini* and *I. pacificus* are distributed in Ontario and British Columbia, respectively, and may harbor the organism there. Two cases of Lyme disease have been reported in Alberta, where *I. sculptus* and *I. augustus* are the only native ixodid ticks.³¹ Non-ixodid ticks in the United States and Canada may serve as vectors for the transmission of Lyme disease. To a very limited extent *Dermacentor andersoni*, *D. variabilis* (the common dog tick), and *Amblyomma americanum* (the Lone Star Tick) may transmit the disease mechanically. This last species has been incriminated in New Jersey and Texas.⁵⁵ Whether these species become established as vectors will depend on their ability to sustain the spirochete; if they can, the implications for the spread of Lyme disease are impressive, for these species of ticks have a wide range.

In addition to North America, three continents have reported cases of Lyme disease: Asia, Australia, and Europe. In Europe the disease is distributed consistently with the range of *I. ricinus*.^{4, 21, 24, 36, 40, 53} One case has been reported outside the range of ticks and has been attributed to transmission by a mosquito;⁵³ borrelial antibodies have been identified in deer flies, horse flies, and mosquitos in endemic areas.³³ Lyme disease has been found in Hunter Valley, Australia, where no known arthropod reservoir exists, but as other arthropods are discovered to be capable of being infected with, and sustaining, *B. burgdorferi*, it is certainly possible that a vector for Lyme disease in Australia will be identified.^{55, 76}

Human patients are accidental hosts in the two-year tick life cycle, replacing both the definitive host and the intermediate host (Figure 1). The nymph represents the greatest threat to human beings, since it is an aggressive feeder and 30 per cent of *I. dammini* larvae survive to the nymphal stage. However, all stages can feed on human hosts. *Borrelia burgdorferi* is widespread in the animal kingdom, and it is believed that the spirochete is acquired by the tick from an infected host, develops in the midgut of the tick, and is then transmitted by salivation and regurgitation when the tick feeds. The frequency of Lyme disease in a particular region is dependent on the density of ixodid ticks, the rate of parasitism of

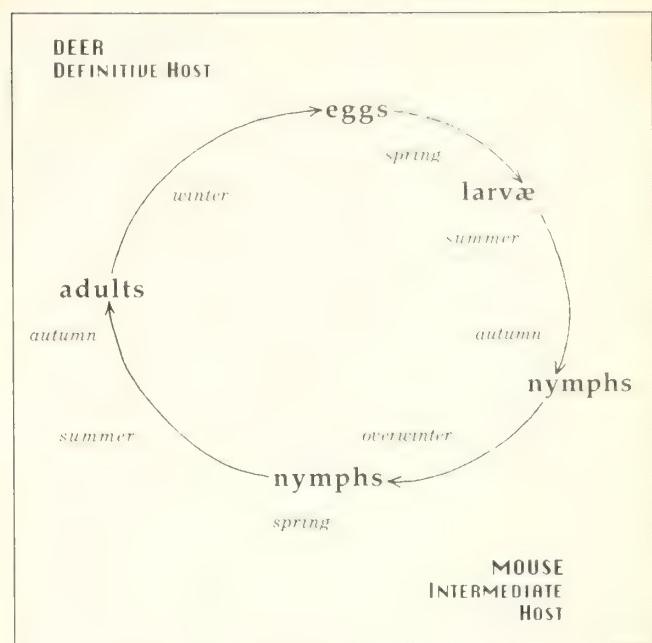


Fig 1. Life cycle of *Ixodes dammini*.

vertebrate hosts by the ticks (ie, the density of ticks on the hosts), and the rate of infection of the ticks by *B. burgdorferi*. The major reservoirs are the white-footed mouse and the white-tailed deer. All stages of the tick parasitise the deer which is the preferred host for the adult tick. However, while the availability of the deer determines the rate of reproduction by adult *I. dammini*, the role of deer as reservoirs for the spirochete remains to be substantiated.³⁹ Nymphal ticks feed more readily on various animals, including mice and other rodents, raccoons, domestic animals, and birds.⁷⁵ Thus, while the distribution of the white-tailed deer may be the determining factor in the distribution of *I. dammini* and of Lyme disease in a typically endemic area, the density of the immature forms parasitising the white-footed mouse may be the variable most important in determining the proportion of ticks infected by *B. burgdorferi* in a given area.^{5, 6, 8, 39, 44, 45, 54}

Borrelia burgdorferi overwinters in the nymph. Because both larvae and nymphs feed predominantly on mice, there are several opportunities for horizontal transmission of *B. burgdorferi* from one tick to the next: the tick may infect the host animal, and another tick in either the larval stage or the nymphal stage may then acquire the pathogen during its blood meal. If the number of available mice is reduced, a greater number of nymphs would parasitise each mouse, thus increasing the risk of horizontal transmission of *B. burgdorferi* from one nymph to another. If the

mice are plentiful and the tick population stable, then the population of vectors might be diluted, reducing the risk of horizontal transmission to a non-infected tick.^{28, 39} The density of the tick population and the proportion of infected ticks vary considerably from one endemic area to another. After deforestation and consequent decimation of the white-tailed deer herd, *Ixodes dammini* was originally found only on Naushon Island off the Massachusetts coast prior to 1949. Its range now includes many areas in which the white-tailed deer has reappeared in southern New England and the Mid-Atlantic states.³⁹ As many as 100 per cent of the ticks on the large islands off the coast of Massachusetts may be infected. In the US, infection of ticks by *B burgdorferi* varies from one to two per cent in *I pacificus* in the west in 1985¹³ to approximately 60 to 75 per cent in *I dammini* in southeastern Connecticut and Massachusetts and Shelter Island, New York⁶⁸ — hence the greater number of cases of Lyme disease along the eastern seaboard.

Other arthropods, e.g., deer flies, horse flies, and mosquitos,³³ may be potential mechanical vectors, if not true hosts, and may prove to be a factor in transmitting Lyme disease in a highly endemic area.

Epidemiology

The true incidence and exact prevalence of Lyme disease in the United States are unknown. Lyme disease has been reported in people of ages 1 to 90 years in Rhode Island, but this distribution is limited by exposure to the tick. Probably for this reason, the risk of infection diminishes after the fourth decade.⁶¹ Distribution between sexes is approximately 1:1, although in some states slightly more males than females acquire Lyme disease, possibly as a result of increased risk of tick bite in work or recreation.

The majority of cases in northeastern and mid-western states are diagnosed between April and December, consistent with an incubation period of 3-40 days following the season during which *Ixodes dammini* larvae moult into nymphs. Data from Great Island, Massachusetts, and Fire Island, New York, along with observations of the typical variations in the presentation of patients with Lyme disease (neurologic, cardiac, or arthritic manifestations or combinations of these) suggest that subclinical infection is common and that untreated patients are at risk for late complications.^{23, 75}

Distribution of Lyme disease in Rhode Island and Connecticut. Each year the reported attack rate

increases: the incidence of Lyme disease in Connecticut in 1985 increased by 163 per cent over that in 1977 to 22/100,000. Town-specific incidences were highest in southern Connecticut, east of the Connecticut River. The peak incidence of Lyme disease in Connecticut, 39 cases/100,000, occurred in five to nine-year-old children followed by a second peak, 28 cases/100,000, in 35 to 40-year-old adults; and the smallest age specific incidence in Connecticut, 11/100,000, was in 20 to 24-year-old adults. The proportion of seropositivity was 444/12,000 (3.7 per cent) in southern Connecticut.³² Figures in Rhode Island suggest that the peak incidence of the disease is in 30 to 34-year-old adults (16.3 per cent of cases occurred in this age group in 1987). Age-adjusted attack rates suggest that the risk of acquiring the illness is similar in all age groups through the fourth decade, decreasing thereafter. However, in Rhode Island, 51.4 per cent of cases in 1987 occurred in females. In Rhode Island, 14.9 per cent of cases in 1986 and 39.8 per cent in 1987 occurred in residents of Providence where approximately 35 per cent of the population resides (Table 1). This may also reflect geographic proximity to hospitals — i.e., incidence in other parts of Rhode Island may be under-reported, relative to Providence.⁴⁹

Table 1. Lyme Disease in Rhode Island January, 1982-July, 1987. (adapted from Brondum J et al.¹⁰)

New Cases by County (n=182)	Cases per 100,000 Population
Bristol County	6.5
Kent County	6.5
Newport County	3.7
Providence County	7.0
Washington County	121.1

In Rhode Island more than 90 cases have been reported in 1988 as of August 31.⁴⁹ While analysis of these cases is not yet complete, there is no reason to believe that there will be a significantly different geographical distribution for the calendar year 1988. The increase in number of cases reported to date in 1988 compared with those reported in 1986 and 1987 is most likely a function of increasing incidence, although enhanced awareness in the lay and medical communities alike has resulted in increased reporting.

Pathogenesis

The spirochete *Borrelia burgdorferi* is present in salivary and faecal excretions of the feeding infected tick and is introduced into the skin or

bloodstream of the patient several hours after the tick has begun to feed. Within 3 to 40 days, the organisms migrate through the skin, producing the pathognomonic primary annular lesion, erythema chronicum migrans (ECM). In some patients the organism is disseminated hematogenously to brain, heart, liver, and spleen, or to other skin sites (producing secondary annular lesions). The organism has been recovered from cerebrospinal fluid in one patient with neurologic abnormalities two and one-half months following the onset of ECM. Therefore, it is possible that at least some of the inflammatory disease within the central nervous system is caused by direct invasion by the spirochete. Rarely does the spirochete survive in joints. Hence the inflammation may be due not only to the presence of *B burgdorferi* itself, but also to a self-perpetuating inflammatory host response to the organism. *B burgdorferi* may be phagocytosed by monocytes and polymorphonuclear leukocytes, but whether they survive within monocytes is not known. The immune abnormalities begin as circulating immune complexes associated with ECM at the onset of illness. Cryoglobulins containing IgM are demonstrable, and there is an elevated serum IgM. This correlates with and tends to predict subsequent involvement of the central nervous system, heart, and joints. Serial determinations of serum *B burgdorferi* IgM levels are a useful laboratory indicator of disease activity, since elevation persists during neurologic and cardiac involvement. But late in the disease, when arthritis occurs, serum IgM levels may be normal, and immune complexes and cryoglobulins are found not in the serum, but localised in synovial fluid. Joint involvement has been shown to be associated with less spontaneous suppressor-cell activity than normal and with enhanced responsiveness of mononuclear cells to *B burgdorferi* and to phytohemagglutinin, especially in joint fluid, concurrent with the elevated total serum IgM level. It is possible that decreased suppression may permit damage to host tissues by either autoimmune phenomena or a heightened response to the spirochete. Among patients who develop either neurologic or joint disease late in the course of the illness, there is an increased frequency of the B-cell alloantigen DR2.^{19, 28, 65} Variations in homology among different isolates of *B burgdorferi* may be related to differences in patterns of illness in Europe and North America.^{2, 50, 77, 81}

The spirochete has been isolated from blood, cerebrospinal fluid, and skin and rarely from joint fluid, but not from cartilage, urine, or lymph

node aspirates. Visualisation of the spirochetes in affected tissues is similarly difficult.

Clinical Presentation

Onset of Lyme disease occurs with the introduction of the spirochete *Borrelia burgdorferi* through the bite of an infected ixodid tick. However, patients may not present with a history of a tick bite even in endemic areas (Table 2). The course of illness that ensues may involve any or none of three stages which may overlap.

Table 2. Lyme Disease Cases Reported to Rhode Island Department of Health January, 1982-July, 1987 (adapted from Brondum J et al.¹⁰)

	Per Cent of Patients (n=182)
Tick-bite within one month prior to onset	37
Erythema chronicum migrans	62
Arthritis	46
Neurological involvement	14
Cardiac involvement	4

Stage I. The first stage begins with a tick bite typically resulting in a small macule or papule which, after a 3-to 40-day incubation period, expands to form the pathognomonic annular erythematous lesion, which has a discrete, often palpable, border: erythema chronicum migrans (Figure 2). Clearing follows from the center towards the border, giving the mature rash a classic bull's eye appearance. In some instances, the expanding lesion remains intensely red. Its coloration may be evenly distributed, or several red rings may be found within the discrete border. The center may turn blue before it clears, or the expanding macular area may be indurated, red, purple, vesicular, or necrotic.⁷¹ The primary lesion may vary in size from 2 cm to 70 cm in diameter and may be warm to the touch, but is often painless.⁶¹ While the exact numbers are not known, it is estimated that approximately 75 per cent of patients with Lyme disease in the United States present with a history of ECM; however, only 48 per cent of children who present initially with arthritis have a history of ECM.^{20, 75}

Non-cutaneous manifestations may include flu-like symptoms, especially fever (mild in adults but often as high as 40°C in children), malaise, fatigue, and local or generalised lymphadenopathy. This initial phase of Stage I Lyme disease in the United States is similar to that described in European patients.

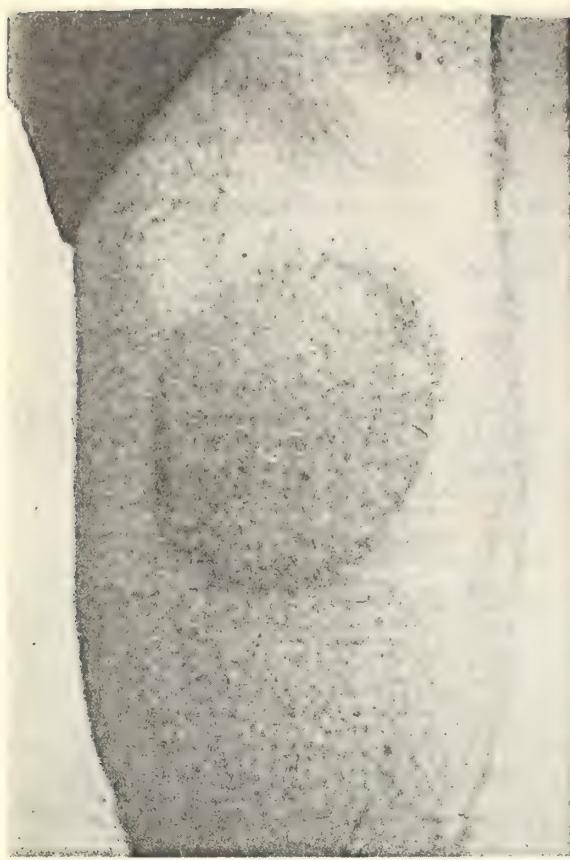


Fig 2. *Erythema chronicum migrans* at site of tick bite.
(Stratton J⁸)

However, about 50 per cent of patients in the United States may progress to a disseminated early illness.⁶¹ Within several days after onset of the initial skin lesion, many patients develop multiple annular secondary lesions. Although these secondary lesions are similar to ECM, they are usually smaller, expand less, and lack indurated centers. Lasting a month or more, they usually spare the palms, soles, and mucous membranes. Unlike many ECM, secondary lesions do not appear to have been caused by the bite of an arthropod.⁷¹ As many as 13 per cent of those with secondary lesions will have more than twenty. Less frequent dermatologic findings include urticaria, diffuse erythema, malar rash, small evanescent red blotches and circles, and septal panniculitis.^{30, 61}

Patients with disseminated Stage I Lyme disease may have, simultaneously or sequentially, intermittent evidence of any of the following signs and symptoms which are usually benign and self-limited: meningeal irritation (excruciating headache, stiff neck), mild encephalopathy, photophobia, dysaesthesia, migratory musculoskeletal pain, hepatitis, generalised lymphadenopathy,

splenomegaly, sore throat, non-productive cough, and testicular swelling (Table 3). Lethargy and fatigue may be constant and incapacitating. These complaints are not associated with a spinal fluid pleocytosis or objective neurological deficit. Musculoskeletal involvement may include arthralgias, myalgias, joint swelling, and painful tendons, bursae, and bones. Although these varied symptoms usually fade within one month (but have lasted as long as 14 months), secondary skin lesions may recur in as many as ten per cent of patients.⁶¹

Presentation in European patients is similar to that in the United States. European erythema migrans usually begins as an expanding annular lesion, often accompanied by central clearing; sometimes a tender lymphocytoma-like lesion, lymphadenosis benigna cutis, is found at the center, most commonly on the head (especially the ear), and may occur as a single lesion or in groups.⁸¹

Stage II. 1) *Nervous system involvement.* Although the neurological symptoms in Stage I are usually benign, several weeks to months after the onset of early Lyme disease, about 15 per cent of patients develop central and peripheral nervous system disease. The usual triad of symptoms consists of Lyme meningitis, cranial neuropathy (especially Bell's palsy), and peripheral radiculoneuropathy; however, any of these may occur alone.⁴⁷ Lyme meningitis is characterised by headache, nuchal rigidity, nausea, vomiting, lassitude, and irritability.^{43, 47} (A similar complica-

Table 3. Early signs of Lyme Disease in Patients Presenting with ECM. (modified from Steere et al.⁶¹)

	Per Cent of Patients
Erythema chronicum migrans	100
Multiple annular lesions	48
Lymphadenopathy	
regional	41
generalised	20
Pain on neck flexion	17
Malar rash	13
Erythematous throat	12
Conjunctivitis	11
Right upper quadrant tenderness	8
Frank arthritis	6
Splenomegaly	6
Hepatomegaly	5
Muscle tenderness	4
Periorbital oedema	3
Evanescence skin lesions	3
Abdominal tenderness	2
Testicular swelling	1

tion occurs in European patients with erythema migrans disease: Bannwarth-Garin-Bujadoux syndrome, which was associated with a history of tick bite, described in 1922.^{2, 4, 50, 77}

The cerebrospinal fluid (CSF) in Lyme meningitis is characterised by lymphocytic pleocytosis and elevated proteins; glucose and opening pressure are normal. In rare instances, *B burgdorferi* has been cultured from the CSF.⁶⁸

Peripheral and cranial neuritides are frequent: as many as 50 per cent of patients with Lyme meningitis have Bell's palsy, unilaterally or bilaterally; and other cranial nerves may be involved. Lyme encephalitis may occur with acute organic signs and symptoms such as memory loss, emotional lability, inability to concentrate, irritability; pseudotumor cerebri and a Guillain-Barré-like neuropathy have also been described.^{9, 43, 46} A British patient has recently been described as having had a purulent meningoencephalitis; his CSF revealed 2750 polymorphonuclear leucocytes and a CSF glucose 2.1 nmol/l.⁹

2) *Cardiac involvement.* Up to ten per cent of patients develop cardiac abnormalities within weeks after the onset of ECM: syncope, dizziness, shortness of breath, substernal chest pain, arrhythmias, pericardial rubs, and S₃ gallops. Electrocardiographic (EKG) abnormalities include fluctuating degrees of atrioventricular block (first degree, Wenckebach, or complete block). An artificial pacemaker may be necessary temporarily.⁶² Myocarditis has been diagnosed by EKG and gallium scan as well as by postmortem examination and endomyocardial biopsy, in which lymphocytic infiltrate, myocytic necrosis, and spirochetes have been demonstrated.^{25, 37} The duration of cardiac problems is usually three days to six weeks. The clinical pictures may resemble that of acute rheumatic fever. However, in Lyme disease complete heart block may be more common, myopericardial involvement tends to be milder, and valves seem not to be affected.⁷¹

3) *Other complications.* Iritis, optic neuropathy, and a panophthalmitis resulting in blindness have been reported.^{20, 51, 61, 64} Persistent recurrent hepatitis has been documented in untreated Lyme disease.²² One patient has been reported to have succumbed to adult respiratory distress syndrome. At autopsy diffuse alveolar damage of the lungs and transformed lymphocytic response were demonstrated. Spirochetes were found in lymph nodes.²⁹

A cutaneous complication reported in European patients is acrodermatitis chronica atroph-

icans. The initial stage is characterised by violaceous discolouration and infiltration of the skin, sometimes with marked swelling. In the atrophic phase, the skin becomes thin, with loss of appendages. The lesions usually spread from distal to proximal sites, and some patients have associated joint involvement or peripheral neuropathy.⁸¹

Stage III. The third stage is characterised predominantly by arthritic and neurological complications.

1) *Joint involvement.* Within a few weeks to two years after the onset of ECM, about 60 per cent of patients develop recurrent asymmetric monoarticular or oligoarticular arthritis, especially in large joints such as the knee. If joint involvement occurs early in the illness, the typical pattern is one of migratory musculoskeletal pain in joints, tendons, bursae, muscle, or bone, often with pain in only one or two sites at a time, a few hours to days in a given location, without joint swelling. Months after the illness, frank arthritis may occur, with intermittent attacks of joint swelling and pain in large joints, especially in the knee. Affected knees are usually more swollen than painful, and are often hot, but rarely red. Baker's cysts occasionally form, with early rupture. In others the arthritis resembles rheumatoid arthritis, symmetrically involving large and small joints.^{65, 66} In fact, rheumatoid arthritis may be the initial impression when the clinical presentation is not associated with a history of antecedent ECM and other characteristic early symptoms.¹⁸ (In a laboratory-based surveillance program in Connecticut, 61 per cent of patients with arthritis did not report antecedent erythema chronicum migrans.)³² Fatigue is common with active joint involvement, but fever and other constitutional symptoms are unusual.⁷¹ Although frank synovitis is infrequent, the picture in children may resemble that of septic arthritis, with high fever and severe synovitis.¹⁹

Ten per cent of patients with Stage III Lyme arthritis will go on to develop chronic arthritis with loss of asymptomatic intervals and with erosive damage especially in the knees, not unlike that in rheumatoid arthritis.⁷¹

Arthrocentesis generally reveals white cell counts varying from 500 to 110,000 cells/mm³, predominantly neutrophils, total protein ranging from three to eight g/dl, C3 and C4 levels usually greater than one-third, and glucose levels usually greater than two-thirds of those in serum. *B burgdorferi*-specific IgG can be demonstrated in synovial fluid. *B burgdorferi* has been isolated

in synovial fluid and visualised by direct immunofluorescent stain. One motile spirochete was retrieved in culture from a patient whose illness had begun with erythema chronicum migrans, followed by a one-year asymptomatic period before the onset of monoarticular arthritis, and who had been treated for seven days with intravenous penicillin at 24 million units per day.⁵⁹

2) *Nervous system involvement.* *Borrelia burgdorferi* has been implicated in serious chronic CNS disease months to years after infection. Some patients are without history of antecedent events typical of Lyme disease. Duffy describes three types of clinical presentations, all associated with high titres of IgG antibody to *B. burgdorferi*:¹⁹ (1) multiple-sclerosis-like demyelinating illnesses characterised by remissions and exacerbations, some with permanent serious CNS damage;^{47, 48} (2) serious psychiatric disorders years later in children, especially those infected prior to the age of ten years; and (3) episodic, often incapacitating, fatigue accompanied by soft neurological signs lasting days to weeks, with symptom-free intervals.⁴²

Lyme Disease in Pregnancy

Infection by *Borrelia burgdorferi* in the pregnant woman poses considerable risk to the fetus; for, as in maternal syphilis, the spirochete has been demonstrated to cross the placenta. Fetal outcome has varied from the absence of problems to fetal demise. The first reported case was an infant who was born with cardiac abnormalities and died. Although transplacental infection of the fetus was documented, spirochetal presence in cardiac tissues could not be demonstrated at autopsy.⁵² Five of 19 cases of maternal infection studied during 1976-1984 resulted in adverse fetal outcome: intrauterine fetal death without congenital anomalies at autopsy, prematurity, syndactyly (type I), cortical blindness with developmental delay, and neonatal rash. Outcome was not related to the timing of maternal infection, which ranged from 6 weeks to 37 weeks of gestation. Cortical blindness with developmental delay occurred in an infant born to a mother contracting the infection at 27 weeks of gestation. (Onset of infection in the 14 other women, the outcome of whose pregnancies were normal, occurred at 2 weeks to 37 weeks of gestation.) In none of these five cases was *B. burgdorferi* cultured; fetal IgM was apparently not measured. (In normal infants born to the other 14 women studied, five cord bloods were assayed for antibodies: in one, polyvalent antibody titre was el-

evated, but subsequently disappeared.³⁸ There was no correlation between history or timing of antibiotic treatment, choice of agent, and fetal outcome.^{38, 80}

Diagnosis

The diagnosis is most easily made by recognition of the pathognomonic rash, erythema chronicum migrans, when it occurs. However, when the rash is not typical or has disappeared and the patient presents with systemic signs and a history which does not well describe the rash, diagnosis may then be more easily accomplished by detection of antibody to *Borrelia burgdorferi*. Recovery of the organism itself from blood, other body fluids, or rash is difficult and is of little use in the diagnosis and management of a patient presenting with a history and physical examination consistent with Lyme disease.^{7, 58}

Serologic testing, either by indirect immunofluorescent assay (IFA) or by enzyme-linked immunosorbent assay (ELISA), remains the most practical available adjunct for diagnosis. Both are quite sensitive and specific, although some authorities favor the ELISA for its purported greater sensitivity and specificity.^{14, 34, 35, 82}

In the natural course of untreated Lyme disease, IgM peaks three to six weeks after infection, coincident with Stage I, and then wanes, while IgG peaks more slowly and is at its maximum during Stage II and Stage III.^{14, 42} Antibody response during erythema chronicum migrans is largely that of IgM and may not be detectable at a significant level by polyvalent IFA at the onset of the illness, probably because the spirochete is still localised to the skin at the site of the rash. In early erythema chronicum migrans ELISA for IgM is probably the more sensitive test. Patients with joint, neurological or cardiac involvement almost always have significant titres ($\geq 1:128$) of IgG by either method.

It is important to recognise the limitations in using a serological test in order to establish a diagnosis. However, if the patient presents in an endemic area with a rash that is typical, then serology, less sensitive in early illness, is not necessary for diagnosis and initiation of therapy. Furthermore, if the patient receives appropriate antibiotic therapy during this stage of the illness, the antibody response may be blunted. When the patient presents, however, without a rash but with systemic illness consistent with early Lyme disease, an IgM level or paired specimens taken four to six weeks apart for polyvalent immunoglobulins will be useful. During the later stages of

Lyme disease a single specimen for IgG or polyvalent immunoglobulins is usually sufficient.

Serological test results should always be interpreted in the context of the clinical presentation. Although false positives are not frequent, they can occur in patients with syphilis (especially in secondary syphilis) and other spirochetal infections and have been reported in patients with infectious mononucleosis.^{14, 68} (Syphilis may be ruled out by VDRL and, if necessary, by FTA-absorption; and acute infectious mononucleosis may be excluded by Epstein-Barr virus titres.)

The Rhode Island Department of Health Laboratories performs the polyvalent immunoglobulins IFA free of charge. A titre performed by the Rhode Island Department of Health Laboratories is considered to be positive at a dilution $\geq 1:128$. If the titre is borderline, a second specimen four to six weeks later is requested. ELISA titres are performed by commercial and hospital laboratories.

Treatment

Stage I. Oral antibiotic therapy is usually effective in reducing the duration of erythema chronicum migrans, systemic symptoms, and joint inflammation, and in preventing later illness and sequelae.⁷² Tetracycline is the drug of choice, when possible, because the complications of later Lyme disease (meningoencephalitis, myocarditis, recurrent arthritis) have occurred less frequently in patients treated with tetracycline than in those treated with erythromycin.^{15, 69}

In nonpregnant, nonlactating women and other patients at least nine years of age, tetracycline 250 mg by mouth four times a day for 10-20 days is the drug of choice. Doxycycline 100 mg by mouth twice daily is an acceptable alternative. Duration of therapy should be extended to the maximum of this range when symptoms do not resolve quickly. When tetracycline is not tolerated, penicillin may be used as it is in pregnant women and children.¹

In pregnant or lactating women recommended therapy is penicillin V 250 to 500 mg by mouth four times a day. In children < 9 years of age the dose of penicillin V is 50 mg/kg/day divided in four doses (not less than 1 g or more than 2 g per day). Amoxicillin 250 mg by mouth three times a day in adults and 20 mg/kg/day divided in three doses in children may be substituted. While the history of antibiotic treatment and the choice of drug has not been correlated to fetal outcome, because pathogenesis in the fetus is not understood, treatment of maternal Lyme disease

should probably be initiated promptly, preferably with penicillin, which crosses the blood-brain barrier in the fetus.

In patients allergic to penicillin, erythromycin 250 mg by mouth four times daily for 10 to 20 days in adults or 30 mg/kg/day in four divided doses in children for 10 to 20 days may be used. It has been suggested that a 15-to 20-day course of erythromycin is preferable to a 10-day course because erythromycin is less effective than penicillin or tetracycline.⁶⁹

The Jarisch-Herxheimer reaction has occurred — more frequently in those patients treated with penicillin or tetracycline than with erythromycin, probably because of the rapid rate of spirochetal killing with these two agents.⁶⁹

Stage II. Another antibiotic, ceftriaxone, has been shown to be effective *in vitro* and *in vivo* against *B burgdorferi*. Its CD₅₀ is similar to that of tetracycline and greater than that of penicillin. Furthermore, because of its half-life (6.5 hours), it can be administered once or twice a day, allowing nearly constant antibiotic levels over a prolonged period of time. (In spirochetal diseases such as syphilis, constant antibiotic levels have been shown to be preferable to peaks because of the long generation time of the organism.) Ceftriaxone penetrates both the meninges and the synovium with levels 60-100 per cent of those achievable in the serum; sustained levels in the CNS and synovial fluids are bactericidal.^{17, 26} Indications for the use of ceftriaxone are included in the outline below.

1) Cardiac disease. Patients with minor conduction system abnormalities (first degree AV block with a PR interval *less than* 0.30 seconds) should be treated with tetracycline, doxycycline, or penicillin V as for Stage I disease. Patients should reduce their activity and be closely monitored. Those with more severe involvement of their conduction systems should be hospitalised, placed on cardiac monitors, and treated with intravenous penicillin G 10 million units per day or ceftriaxone 2 g/day for 10 days. A temporary pacemaker may be required.¹

2) Neurological disease. Patients with mild neurological involvement (such as Bell's palsy alone), may be treated with tetracycline, doxycycline, or penicillin V as for Stage I disease, but duration of treatment should be at least 20 days, possibly as long as one month. Patients with meningoencephalitis or cranial or peripheral neuropathies should be treated with intravenous penicillin G 20 million units per day for 14 days.^{19, 71, 74} Ceftriaxone 2 g/day has been used effectively in pa-

tients not responding to IV penicillin.^{16, 17}

A recent study demonstrated that ceftriaxone may be of use in patients who have not responded to intravenous (IV) penicillin. Two regimens of ceftriaxone were compared: 2 g vs 4 g per day. There was no advantage demonstrated in the use of the larger dose.¹⁷

Stage III. Response to appropriate treatment of Stage III Lyme disease may be slow and may not be apparent for several weeks after therapy.

1) *Arthritis.* While intravenous penicillin 20 million units per day has been shown to be effective in patients with established Lyme arthritis,⁶⁷ ceftriaxone 2 g/day may be more efficacious.¹⁷ Furthermore, ceftriaxone has been demonstrated to be effective in penicillin failures. Nonresponsive arthritis has resolved after a second course of antibiotic therapy, with the same or an alternative agent.¹ Studies comparing the effectiveness of amoxicillin 500 mg by mouth three times daily combined with probenecid 500 mg by mouth three times daily or doxycycline 500 mg by mouth twice daily are presently under way.

The role of steroids in the treatment of Lyme arthritis is unknown. It should be noted, however, that antibiotic treatment failures are more likely when the antibiotic follows a course of intra-articular steroids.⁶⁷

2) *Neurologic disease.* Patients with neuropsychiatric disease, focal central-nervous-system disease, and chronic fatigue syndromes have been treated with intravenous penicillin G or ceftriaxone with varying rates and degrees of effectiveness.^{1, 42}

Prevention

Although investigations of environmental controls are underway, the only means of control at present are avoidance of human infection, and prompt treatment when it does occur in order to prevent chronic illness.

Common-sense measures for decreasing the risk of tick bite and subsequent infection are practical and safe. The tick inhabits low-growing plants and vegetative debris. People living or vacationing in rural endemic areas should be informed about appropriate attire, insect repellants, and methods of tick removal. Boots or shoes with socks, light-colored trousers tucked into the boots or socks, and light-colored shirts are advised. A light color is practical because it provides a background against which the small tick may be visualized (unengorged nymphs appear not much larger than 1-2 mm dark specks). Since ixodid ticks inhabit low vegetation (unlike the

Table 4. Antibiotic therapy of Lyme Disease.

Stage I	Duration
Drug of choice	
Tetracycline 250 mgm p.o. q.i.d. or Doxycycline 100 mgm p.o. b.i.d.	10 to 20 days
Children, pregnant and lactating women	
Penicillin V 250-500 mgm p.o. q.i.d. 50 mgm/kgm p.o. per day divided q6h or Amoxicillin 250 mgm p.o. t.i.d. 20 mgm/kgm p.o. per day divided q8h	10 to 20 days
Patients not tolerating tetracyclines or penicillins	
Erythromycin 250 mgm p.o. q.i.d. 30 mgm/kgm p.o. per day divided q6h	20 days 20 days
Stage II	
Cardiac disease	
First degree AV block with PR<0.30 secs as in Stage I	10 to 20 days
More severe conduction abnormalities	
Penicillin G IV 10 million units/day or Ceftriaxone IV 2 gm/day	10 days 10 days
Neurological disease	
Mild, such as Bell's Palsy alone as in Stage I	≥20 days
Meningoencephalitis, other cranial or peripheral neuropathies	
Penicillin G IV 20 million units/day IV 250,000 units/kgm per day if fail to respond Ceftriaxone IV 2 gm/day IV 100 mgm/kgm per day	10 to 14 days 14 days
Stage III	
Arthritis and neurological disease	
Ceftriaxone IV 2 gm/day or Penicillin G IV 20 million units/day	14 days 14 to 21 days

dog tick which can be found on higher bushes), it is essential to protect the feet and lower legs. Small children, because they are short, are at greater risk for tick attachment on the upper portion of their bodies, especially the head and neck. Tick repellants containing N,N-diethyl-m-toluamide ("deet") in as high a concentration as 100 per cent are available: probably 30 per cent is adequate and may be safer. Insect repellants containing 0.5 per cent permethrin are marketed, but are not so readily available as those with "deet" alone. This concentration of permethrin has been shown to be effective against all life stages of the ixodid ticks.⁵⁶

The tick requires as many as 96 hours to feed. Therefore, systematic searches over the entire

body surface for ticks are recommended, certainly no less frequently than once a day. (In children, searches should cover the head and neck.) When found, a tick may be removed by grasping its head with fine pointed forceps and exerting steady slow traction perpendicular to the surface of the skin.⁴¹ In order to prevent regurgitation of gut contents, one must be careful not to squeeze the tick's abdomen too vigorously. Cleansing of both the site of attachment and the hands with soap and water is advisable because salivation may last several minutes after the tick is removed. The person removing the tick is thus also at risk for infection. If the tick is to be preserved for identification, rubbing alcohol is a readily accessible medium.

People bitten by any species of tick should be encouraged to record the date. If symptoms appear within six weeks, knowledge of the species of tick and date of the bite and history and physical examination will aid the physician in diagnosis of any of the tick-borne diseases in Rhode Island, all of which may present initially with vague flu-like symptoms: Lyme disease, Rocky Mountain spotted fever, and babesiosis.

Summary

Lyme disease, a newly recognised borreliosis with both acute and chronic features, is still not well understood. While it is an infectious disease endemic in certain regions, especially in New England, it bears resemblance to some immune-mediated arthritides. Neither the exact prevalence nor the incidence is known. However, surveillance programs clearly demonstrate not only that the numbers of those affected are increasing, with or without symptoms, but also that the range of the vector in this region, *Ixodes dammini*, is enlarging. Improved case reporting by physicians can increase effectiveness of surveillance, allowing definition of patterns of illness and identification of pockets of endemicity. Diagnosis of early Lyme disease is straightforward when patients present with the pathognomonic rash, erythema chronicum migrans. Therapy should be promptly initiated in these patients. For patients presenting with atypical illness or late disease, serological tests are readily available.

Because of the large number of species which serve as hosts it is unlikely that we shall have a program of control in the near future. Therefore, the two feasible means are the avoidance and removal of ticks and treatment of the clinical disease in the human host when it occurs. While recognition of the pathognomonic rash and

prompt appropriate therapy by medical practitioners will reduce the risk of many of the deleterious sequelae of late Lyme disease, it will not necessarily prevent adverse fetal outcome in the event of maternal infection. A population educated in techniques for avoidance of ticks and infection and in the need for prompt diagnosis and treatment may be more efficient in reducing the risk of complications.

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Lyme Borrellosis and Other Tick-borne Diseases in Rhode Island

Lyme Disease Is Probably Much More Prevalent Than We Have Thought in the Recent Past

Kerwin E. Hyland, PhD
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Lyme disease is a zoonotic affliction caused by the spirochete, *Borrelia burgdorferi*, and transmitted principally by several species of ticks of the genus *Ixodes*. Early symptoms include the formation of a characteristic circular expanding red rash at the site of the tick bite, and flu-like symptoms.¹ Cardiac^{2,3} and neurologic^{4,5} manifestations may develop later followed by chronic arthritis.⁶

Historical Review

Erythema chronicum migrans (ECM), a skin rash that usually follows the bite from a spirochete-infected tick, was first described by Afzelius⁷ in Sweden. Many speculations on the causative agent

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for ECM in Europe were advanced. Lipschutz⁸ thought of microscopic microorganisms which may be transmitted via the tick's intestinal and salivary secretions; Linnhoff⁹ observed spirochete-like organisms in skin lesions removed from ECM patients. Hollstrom¹⁰ suggested that ECM is due to infective microorganisms which cause allergies and are transmitted by ticks.

The first documented case of ECM in the United States was reported in 1970 in Wisconsin.¹¹ An outbreak of "Juvenile Rheumatoid Arthritis" was reported from southern Connecticut in 1975. The clinical symptoms of this illness were later collectively described as "Lyme disease" or "Lyme arthritis."¹

Although the disease was clinically described, the etiologic agent was not yet known. Many efforts to reveal the identity of the causative agent were unsuccessful.¹² Positive correlation between the distribution of the deer tick, *Ixodes dammini*, and Lyme disease was established, particularly in the Northeast.¹³ Accidentally, while conducting a survey on tick/rickettsial diseases on Long Island, NY, Dr Willy Burgdorfer and his colleagues observed poorly stained spirochetes from the intestinal tract of a female *I. dammini*.¹⁴ Further investigations revealed the presence of such organisms in both nymphs and adults of this tick.¹⁵ Moreover, in Europe the sheep tick, *Ixodes ricinus*, was found to harbor similar spirochetes.¹⁶ Serum obtained from Lyme disease patients was found to react positively with spirochetes isolated from *I. dammini*.¹⁷ The spirochete was subsequently de-

scribed and named *Borrelia burgdorferi* in honor of its discoverer, W. Burgdorfer of the Rocky Mountain Laboratory in Hamilton, Montana (Figure 1).¹⁸

Global Distribution of Lyme Disease

Lyme disease is concentrated in the Northeast (Rhode Island, Connecticut, Massachusetts, New York, and New Jersey),¹⁹⁻²² the West (California, Oregon, Nevada, and Utah)^{23, 24} and Northern Midwest (Wisconsin and Minnesota)²³ parts of the United States. At least 32 states have reported Lyme disease cases. Almost all European countries including France,²⁵ Italy,²⁶ Germany,²⁷ Austria,²⁸ Belgium,²⁹ England,³⁰ the Soviet Union,³¹ Sweden,³² Switzerland,³³ Hungary³⁴ and Czechoslovakia,³⁵ as well as Canada^{36, 37} and Japan,³⁸ have reported indigenous Lyme disease cases. Recently, spirochetes similar to those of *B. burgdorferi* were isolated from patients, ticks, and animals in China.³⁹



Fig 1. *Borrelia burgdorferi* from the gut contents of the deer tick, *Ixodes dammini*. 1370X.

Lyme Disease in Rhode Island

Rhode Island harbors a significant amount of the disease. Between 1982-1987, 163 Lyme disease cases were reported to the Rhode Island Department of Health.⁴⁰ Because of under reporting, this number certainly does not reflect the actual incidence of the disease in Rhode Island.

Borrelia burgdorferi was isolated from white-footed mice and meadow voles collected on Patience and Prudence Islands.⁴¹⁻⁴⁴ Furthermore, all the life stages of the deer tick collected from Prudence Island were found to carry the spirochete.^{41, 44, 45}

Tick Vectors for Lyme Disease

Presently, five tick species belonging to the genus *Ixodes* apparently serve globally as the major vectors for Lyme disease: In the Northeastern and Northcentral United States the deer tick, *I. dammini*,^{46, 47} in the West, *I. pacificus*,¹⁹ in the South, *I. scapularis*,⁴⁸ in Europe, *I. ricinus*,⁴⁹ and in China and Japan, *I. persulcatus*,^{38, 39} respectively.

Medical Importance of Ticks

Ticks, next to mosquitoes, are the most medically important arthropods. They are not only annoying pests, but transmit a number of disease agents to man, his livestock, and his pets.

With the advent of Lyme disease, there was a flurry of activity in the Northeast and elsewhere in an attempt to better understand the tick-host preferences, seasonal activity, and ecological patterns of these parasites, all with the goal of shedding light on the epizootiology of this malady. The discovery by Spielman et al⁴⁷ that the deer tick of the Northeast, heretofore identified as *I. scapularis*, was in reality a distinct species, *I. dammini*, brought into focus the need for more detailed study of the biology of ticks. Since then, tick literature has increased manyfold. Some studies have dealt more with the vertebrate host relationships,⁵⁰⁻⁵³ while others have concentrated on *I. dammini*, its hosts, and seasonal activity.⁵⁴⁻⁵⁶ While most work has dealt with the mammalian hosts, avian hosts and their potential for playing a role in the epizootiology of the disease has not been overlooked.^{57, 58}

The fact that attached ticks frequently go unnoticed, especially when in the immature larval and nymphal stages, is reason enough for anyone who is active out-of-doors to anticipate the day when one or more specimens of *I. dammini* will attach and go undetected for a period of time.

Since Lyme disease is the primary concern and the most frequently encountered tick-borne malady in the Northeast, where *I. dammini* is the incriminated tick, we must not lose sight of the other ticks and the additional diseases.

Along with Lyme disease, babesiosis, a malaria-like protozoan parasite is also vectored principally by the same nymphal *I. dammini*.^{59, 60} The causative agent, *Babesia microti*, is found in such reservoir hosts as the white-footed mouse (*Peromyscus leucopus*) and the meadow vole (*Microtus pennsylvanicus*)⁶¹ in coastal New York and southern New England. In human victims it is frequently overlooked or misdiagnosed and can be

fatal in splenectomized individuals.⁶²

The Powassan encephalitis (POW) virus might be considered an "emerging disease" in forested areas of Canada and northeastern United States. This virus has been known only since 1959, when it was reported in a fatal case of encephalitis in a farm boy.⁶² Additional cases continue to be reported, and research indicates that a variety of small-to medium-size mammals serve as hosts, and that various ixodid ticks, including *Dermacentor variabilis*, *Ixodes cookei*, *Ixodes marxi*, and *Ixodes pacificus*, serve as vectors.⁶³

Rocky Mountain Spotted Fever (RMSF) continues to be present in considerable numbers in the Eastern United States. Although the total number of cases fell from 755 reported cases in 1986 to 592 in 1987, the incidence in Maryland rose from 29 to 46 during this period. In 1987, four cases were reported among residents of New York City who had not traveled outside the city within three weeks prior to clinical manifestations.⁶⁴ From 1976 to 1986 there were 17 serologically confirmed cases of this disease in Rhode Island.⁶⁵ In the eastern US this rickettsial agent classically passes from reservoir to human host via the American dog tick (*Dermacentor variabilis*). However, in Newton, CT, an endemic area, three species of ticks were found positive for the rickettsial organism, ie, *D variabilis*, *I cookei*, and *I texanus*. Serum samples from mice were positive for the rickettsial antibodies.^{66, 67}

Tick-borne relapsing fever, although vectored by soft, not hard ticks (Family Argasidae vs Ixodidae), is found primarily in the western part of the United States and should be called to the attention of campers, hunters, and tourists who might employ tick infested buildings. Intermittently feeding soft ticks of the genus *Ornithodoros* are incriminated, but, inasmuch as they do not remain attached to their host, their presence frequently goes unnoticed.

Colorado Tick Fever (CTF) is also associated with campers and hikers and is a viral disease vectored mainly by *D variabilis* in the western part of the country, particularly in Colorado. Apparently the disease frequently goes undetected or undiagnosed; consequently its presence may be greater than the literature would indicate. Approximately 200 cases are reported yearly. It can survive in human victims up to four months.⁶²

Tularemia, a bacterial disease, is sometimes associated with hematophagous arthropods, including ticks. A total of 170 cases was reported in the US in 1986.⁶⁸ It is not a serious problem in the Northeast. Ticks which have been incriminated

include those of the following genera: *Dermacentor*, *Amblyomma*, *Ixodes*, *Haemaphysalis*, and *Rhipicephalus*.

Tick Paralysis due to a toxin produced by the salivary glands may be encountered in the southern and western United States and is associated primarily with *D variabilis* and *Dermacentor andersoni*, respectively.⁶⁹

Several other enzootic tick-borne infections which may be of interest include: (1) Connecticut virus, a disease of the cottontail (*Sylvilagus floridanus*) which is associated with the rabbit tick, *Ixodes dentatus*.⁷⁰ While there seems little danger for human infection, it must be considered, because several species of ticks share rabbits and humans. (2) Ehrlichiosis is an affliction with 46 known cases caused probably by *Ehrlichia canis* and transmitted by the brown dog tick, *Rhipicephalus sanguineus*. Again, this tick does not normally feed on man, but other ticks which attach to dogs, including *D variabilis* and *I dammini*, might passively vector the microorganisms. Of 46 cases reported in the United States, 63 per cent had a prior tick exposure.⁷¹

Ticks of Rhode Island and the Northeast

Faunistic studies of ticks, their hosts, and seasonal distribution have been of general interest to entomologists. Beginning in 1945, Bequaert⁷² gave a comprehensive treatment of the fauna of the Northeastern United States and Canada. Since at that time the nymphs of some of the species were unknown, this paper lacked a key to larvae of the genus *Ixodes*. Cooley and Kohls⁷³ in the same year (1945) did not include a key to the larvae in their major treatise on the genus *Ixodes* in North America. However, in 1961 Clifford et al⁷⁴ published a study on the larval ixodid ticks in the Eastern United States, including a key to the known species.

State and regional studies were also carried out during the ensuing years, including those of Hyland and Mathewson,⁷⁵ who listed 10 species of ticks from 20 different mammalian host species in Rhode Island, while Good⁷⁶ listed a series of mammals and birds as hosts on eastern Long Island and discussed their seasonal distribution. Sonenshine and Stout⁷⁷ compared the fauna from mammals in the Piedmont with those in the coastal plain habitats of Virginia.

Taxonomy and Morphology of Ticks

Ticks are members of the phylum Arthropoda, class Arachnida, which includes mites, scorpions, pseudoscorpions, and spiders. Hard ticks (family

Ixodidae) are characterized by the presence of a dorsal scutum or shield and possess a hypostome, a holdfast organ fitted with backwardly directed teeth, which is inserted into the skin of its host (Figures 2, 3, and 4).⁶⁹ Their life history involves three distinct feeding stages: the larva with three pairs of legs, the nymph with four pairs of walking appendages, but lacking a genital pore, and the adult (including the male and the female), which possesses four pairs of legs and a genital pore. The male is easily differentiated from the female by the presence of a scutum which covers most of its dorsal side.

Some 800 species of ixodid ticks are known worldwide, of which about 60 are known from the United States. They are exclusively parasitic and feed only on vertebrate blood.



Fig 2. Scanning electron micrograph of hypostome of *Ixodes dammini* female. 200X.

Life Cycle of the Deer Tick, *Ixodes dammini*

The deer tick, *I. dammini*, is a three-host tick species which takes two or possibly more years to complete its life cycle (Figure 5).⁷⁸ This tick takes three blood meals as the sole nutrient throughout its life cycle, and each of three trophic stages — larva, nymph, and adult — feed only once. The hosts which they parasitize vary from small rodents and birds to large mammals including human victims.

It is generally understood that the eggs of this tick species are deposited in the spring by the overwintering female and that they hatch into the six-legged larval form within a short period of time. The larvae are most abundant from July through September and virtually disappear during the rest of the year.⁷⁹ They seek and attach mainly to a small mammal or bird. In the North-



Fig 3. Scanning electron micrograph of hypostome of *Ixodes dammini* nymph. 200X.

eastern United States, including Rhode Island, the primary host is the white-footed mouse, *P. leucopus*,^{80, 81} but other mammals and any one of the several ground-feeding or nesting birds are acceptable.^{57, 82} Larval ticks most frequently attach in the summer or early fall and drop from the host when replete. They may remain in the soil and leaf litter throughout the winter and molt the following spring into the eight-legged nymphal form.⁷⁸ The nymphs attach to a host during May, June, or July. This host may be the same small mammal or bird species employed by the larva, or possibly a larger mammal including man. No larger than a pinhead, the nymph is the form most responsible while engorging for transmitting the microbes to human victims. The nymphs feed for a few days or until replete, then detach and drop to the ground, transform into the adult male or female ticks, thus completing the life cycle. The adults are basically active during the fall, but also throughout the following winter and early spring, whenever the warm temperature permits activity. Although foxes (*Vulpes*

spp.), raccoons (*Procyon lotor*), domestic dogs, and even human subjects are acceptable hosts for blood meals,⁸⁴ females prefer feeding on the white-tailed deer, *Odocoileus virginianus*. Males sometimes attach by their mouthparts to mammalian hosts, but never become engorged with blood.⁷⁸ They remain on the host and wait for the female to mate. It is suggested that a large population of deer will maintain an abundance of *I. dammini*.⁸⁵



Fig 4. *Ixodes dammini* female, scanning electron micrograph. 30X.

Mode of Lyme Disease Transmission

Ticks salivate copiously during feeding⁸⁶ and this can serve effectively as a vehicle for transmission of infectious agents. In fact, the Lyme disease-causing agent, *B. burgdorferi*, has been most frequently found in the lumen of the digestive tract of *I. dammini*, where it was first discovered by Burgdorfer.¹⁵ Although spirochetes cannot infect the salivary glands without passing through the hemocoel, they do disseminate during the brief span of time the tick is attached. As Ribeiro et al⁸⁷ pointed out, dissemination to the salivary

glands seems to occur progressively after attachment of the tick, while movement through the hemolymph is a prerequisite to the salivary delivery of an infectious agent. The authors suggested that prompt removal of attached vector ticks appears to reduce risk of infection by the agent of Lyme disease.

Transovarial passage of *B. burgdorferi* to the next generation of larvae has been demonstrated, but such vertical transmission seems not to be significant.⁸⁸⁻⁹⁰ Only 0.7 per cent (2 of 274) of the *I. dammini* larvae were positive for the spirochete via transovarial passage.⁸⁸ Ribeiro et al suggested that such passage is of limited importance in maintaining *B. burgdorferi* in nature, but that it may provide a mechanism for transporting the spirochete to new sites. Undoubtedly, the white-footed mouse is considered as the reservoir host of the spirochete.⁸¹ Since such a low number of larvae are positive for the spirochete, the larvae probably do not transmit the illness, but instead acquire the infection when they feed on the infected reservoir hosts. Larvae harboring the spirochete pass the microbe transstadially to the resulting nymphs, which pass it to the adult stage. In nature the infected nymphs are capable of transmitting the spirochetes to uninfected hosts including man. Nymphs which are yet uninfected may acquire the spirochete from a positive host. After molting and feeding as infected adults, they can transmit the infection to uninfected hosts.

The nymphs are active during late spring and summer.⁹¹ Most persons who contract Lyme disease have been bitten by the nymphal stage of *I. dammini*. Though the tick bites and the disease infection can occur at any time throughout the year, the peak time for Lyme disease infection is May through August when people tend to be outdoors frequently.

Reservoirs of Lyme Disease: Mammalian and Avian

Borrelia burgdorferi was isolated from several wild mammals and bird species. Mammals including the meadow vole (*M. pennsylvanicus*), white-footed mouse (*P. leucopus*), woodland jumping mouse (*Napaeozapus insignis*), eastern chipmunk (*Tamias striatus*), red squirrel (*Tamiasciurus hudsonicus*), grey squirrel (*Sciurus carolinensis*), raccoon (*P. lotor*), and the white-tailed deer (*O. virginianus*) were found infected with the spirochete.^{57, 83, 92-94}

Many authorities have confirmed that *P. leucopus* is the major reservoir host for the Lyme disease spirochete.^{57, 81, 93} This mouse species lives

Life Cycle of *Ixodes dammini*

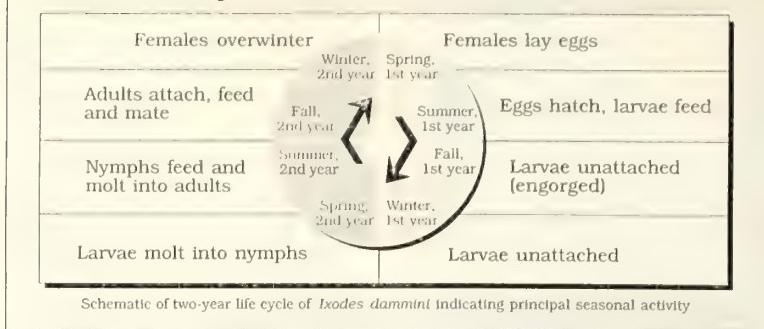


Fig 5. Seasonal life cycle of *Ixodes dammini*.

in close proximity with the deer and may be the most abundant species in wooded habitats. Moreover, it appears that this mouse is the preferred host for both the larval and nymphal stages of the deer tick (Figure 6).

It was demonstrated experimentally that *B burgdorferi* persists in white-footed mice for up to two months after infection.⁹⁵ Field studies showed that the spirochete was present in field-captured mice throughout the year and that it can survive through the winter in both the mouse and the deer tick. Thus, the mice represent an indispensable source of Lyme disease spirochetes. Other mammals may harbor the organism, but only a few (horses, dogs, and rats) show signs of the disease, especially arthritis.⁹⁶⁻⁹⁸

The presence of both the white-tailed deer and the white-footed mouse in certain habitats is of epidemiological significance, where the disease may reach near epidemic proportions. Both animals are the preferred hosts for *I dammini*. The white-footed mouse is a competent reservoir host for *B burgdorferi* and the white-tailed deer provide the female tick with a blood meal necessary for completion of the life cycle.

Because larval and nymphal ticks are known to parasitize a variety of birds, particularly ground-feeding and nesting passeriformes, the role which an avian host might play in the dissemination of both ticks and spirochetes has been investigated.^{52, 58, 82, 99} Spirochetes were found in five species of birds in East Haddam, CT, but these organisms were not cultured or identified. Thus they could have been *Borrelia anserina*, another species known to occur in birds. Later *B burgdorferi* was isolated from the veery (*Catharus fuscescens*) and from *I dammini* taken from a rose-breasted grosbeak (*Pheucticus ludovicianus*) and a common yellowthroat (*Geothlypis trichas*).⁵⁸ The authors conclude that *B burgdorferi* is, in fact, infectious to birds as well as mammals and that

birds seem to be a natural means of disseminating the microbe within and among continents.

Other Hematophagous Arthropods

A number of hematophagous arthropods were found to harbor *Borrelia burgdorferi* in Lyme-disease endemic areas. Four mosquito species (*Aedes canadensis*, *Aedes stimulans*, *Aedes triseriatus*, and *Aedes vexans*), four species of deer flies (*Chrysops callidus*, *Chrysops macquarti*, *Chrysops univittatus*, and *Chrysops vittatus*), and five horse-fly species (*Hybomitra epistate*, *Hybomitra hinei*, *Hybomitra la-siophthalma*, *Tabanus lineola*, and *Tabanus pumilus*), all of the family Tabanidae, were infected with Lyme disease spirochetes.^{100, 101}

Despite the presence of *B burgdorferi* in mosquitoes, it was shown experimentally that the spirochete survived for less than six days in the mosquito tissues. Furthermore, infected mosquitoes fed on spirochete-free hamsters failed to transmit the spirochete. It appears that mosquitoes are not suitable hosts for the Lyme disease spirochete and do not contribute to the epidemiology of the disease.¹⁰¹ However, it is still questionable whether deer flies and horse flies can act as mechanical carriers for the spirochete.

The American dog tick, *D variabilis*, is frequently encountered throughout much of Rhode Island and other parts of the Northeast. This is also a three-host tick species which in the larval, nymphal, and adult stages must have three blood meals from a host. Adult ticks are abundant in spring and early summer. Both male and female attach and suck blood. Dogs seem to be a preferred host for the adults, while human victims are at best a second choice. However, both wild and domestic animals, including fox, skunk, raccoon, woodchuck, horse, cow, and sheep, are acceptable. The female drops to the ground when replete and, after a preoviposition period, lays eggs which hatch to larvae after several weeks.

The larvae feed mainly on small mammals, and choose the meadow mouse as their preferred host. When engorged, the larvae drop from their hosts and metamorphose to the nymphal stage after several weeks. Nymphs attach to the same or larger-sized hosts, feed to repletion, drop to the ground, and molt into the adult male or female.



Fig 6. White-footed mouse (*Peromyscus leucopus*) with larval and nymphal *Ixodes dammini*. 6X.

The adult stage then chooses a larger-sized host for a blood meal. Although the larval and nymphal stages of *D. variabilis* were found attached to and feeding on Lyme disease-infected mice, the adults are rarely observed harboring the spirochete. Apparently, transstadial transmission of the spirochete from the subadults to the adult stage does not occur. This may be explained as a lack of suitable microenvironment in the American dog-tick tissues for growth and survival of the spirochetes.

Tick Control

Controlling or reducing the populations of ticks capable of transmitting diseases to man and other animals should result in a reduction in the risk of acquiring tick-borne infections. The different strategies used, including chemical, ecological, and biological control, will depend on their behavior, habitat, host preferences, presence of natural enemies, and susceptibility to chemicals and habitat changes.

1. *Ecological Control.* The destruction of vegetation in highly endemic areas by burning reduced the abundance of the adult deer tick by 88 per cent during one year after the actual burn-

ing, but later the tick population began to return.

2. *Chemical Control.* Permethrin in pressurized spray at 0.5 per cent concentration applied to clothing yielded 100 per cent protection against all developmental stages of *I. dammini* ticks after one minute post application. A repellent, "deet," provided protection up to 92 per cent when used at a concentration of 30 per cent.¹⁰³ Recently, permethrin spray was approved in Connecticut as a protective agent against tick bites.

Application of carbaryl and diazinon on vegetation reduced the adult *I. dammini* population by 97.1 per cent and 100 per cent respectively. The population of the adult deer tick was reduced considerably post application from the fall to the following spring, the months when the adult ticks are abundant.¹⁰⁴ This is a rather costly control operation because such procedures should be repeated annually, especially in highly endemic areas. In addition, the use of large amounts of acaricides may persist in the environment. The effectiveness of these two acaricides on the subadults of the deer tick is not known. Both stages usually occur under the foliage and are not exposed thoroughly to the action of the pesticide.

Sonenshine and Haines¹⁰⁵ introduced a modified "baited pesticide treatment stations" for controlling the American dog tick. This technique attracted small mammals, (eg. mice, and voles) to a baited box. While in the trap, they coated themselves with dust or oil containing pesticides. A remarkable reduction in tick attachment to small mammals was observed after repeated trials. The "bait box" should be rebaited regularly to attract mammals. Its value in reducing the population of *I. dammini* ticks infesting mice is not known.

Mowing the vegetation resulted in similar observations. Destruction and elimination of the white-tailed deer in tick-infested areas reduced the abundance of larval *I. dammini* during the summer following deer reduction. The abundance of nymphs declined gradually in the course of six years.¹⁰² On the other hand, adult deer ticks were more abundant after being denied the deer hosts. Deer removal is a very controversial issue; humane societies and animal activists denounce such procedures. In addition, the adult deer tick may seek other large or medium-sized mammalian hosts as the deer population declines.

Mather et al¹⁰⁶ introduced an innovative concept for reducing the risk of Lyme disease. Based on the findings that the white-footed mouse is

the major reservoir host for the disease-producing spirochetes and also the chief host for both larval and nymphal stages of the deer tick, their approach was to control these stages, especially the engorging larvae which would subsequently molt into nymphs capable of transmitting *B burgdorferi*. Cardboard tubes (20 × 3.8 cm) filled with 10 g of cotton balls which had been previously impregnated with permethrin were used. Making use of the behavioral pattern of the white-footed mouse whereby the mouse employs the cotton balls along with other materials in constructing its nest, the ticks were exposed to the acaricide. An average of 72 per cent of mice trapped in treated locations were free of any tick infestations, compared with an almost 100 per cent infestation rate in untreated areas.

3. *Biological control.* Among the various control strategies which have been undertaken, the use of natural enemies of ticks as a biocontrol method seems promising. Cookey and Davey¹⁰⁷ reported the predation of cattle fever ticks by hispid cotton rats. Meanwhile, they reviewed the other vertebrate predators of ticks including mammals, birds, and reptiles. Earlier studies established that an entomophagous wasp (*Hunterellus hookeri* or a closely related species) is a parasitoid of ticks.^{108, 109} This wasp has been found in several tick species where it parasitizes only the nymphal stage. The female wasp seeks out a host, inserts her ovipositor, and lays several eggs. These wasp eggs will not develop until the tick has finished its blood meal. The wasp completes the life cycle in the nymphal tick and emerges as an adult, causing the tick's demise. Mass release of this wasp was proposed as a possible measure to reduce the abundance of ticks on Naushon Island, MA,¹¹⁰ in Montana, Colorado, Idaho, Oregon,¹¹¹ and on Capers Island, SC.¹¹² The wasp became established in tick populations following mass release programs.¹¹³ More recently, Mather et al¹¹⁴ indicated that wasp parasitism of *I dammini* does result in its mortality and suggested that parasitism of the tick may, indeed, reduce the intensity of transmission of tick-borne pathogens. Although the wasp is considered indigenous to North America, specimens brought from France were released on Naushon Island, MA in 1926 in an attempt to reduce the population of *D variabilis* there.¹¹³ In Rhode Island, the wasp is now known to exist, at least on Prudence Island. Further study establishing the distribution of the wasp throughout the state and the possibility of utilizing the wasp in a biocontrol strategy is in progress.

Environmental and Cultural Factors Favoring Lyme Disease Transmission

Undoubtedly, Lyme disease emerges as a result of man-made changes in his surrounding environment.^{115, 116} The relocation of the white-tailed deer in certain areas where its population was on the verge of extinction reintroduced *I dammini* along with the deer. The abundance of the deer tick went unnoticed for a long period. During this time the tick population was also in the process of increasing to its full breeding capacity. The disease was perhaps present at the lowest level in wild animals, and the transmission was also at its minimum.

The number of deer increased rapidly over the past 25 years. For example, Block Island was deer-free for many years, until in the 1960s the white-tailed deer was reintroduced to that island. Presently, Block Island is one of the major Lyme disease foci in Rhode Island.

About five per cent of Rhode Island consists of state wildlife lands. Such proportion may provide an unlimited breeding area for the ticks associated with mammals and birds, including *I dammini*. In addition the dream for many having a vacation or retirement home in the woods has many epidemiological ramifications. Lyme-disease-infected nymphs were found on lawns of the houses of Lyme disease patients near woodlands.²¹ Both white-tailed deer and the white-footed mice are nocturnal animals and, while foraging, may drop some of their attached ticks in the vicinity of nearby houses.

Recreational camping, and other field-related leisure activities in endemic areas are also of epidemiological significance. Many people vacation on Block and Prudence Islands, especially during the nymphal season of *I dammini*. We have records of Lyme disease patients living in other states where the risk of Lyme disease is low, who may have acquired their infections while vacationing on these islands. Furthermore, workers (e.g. rangers, wood cutters, and construction workers) in forested land areas are at a higher risk, since they are more frequently exposed to tick bites.

All of these changes, including cultural and environmental factors are of importance in understanding the continuous changes of the tick-borne diseases of humans.

Serodiagnosis

Serological evidence is frequently employed to confirm the clinical diagnosis for Lyme disease. Various techniques can be employed for detection of spirochetal infections in the patient, ver-

tebrate reservoir and arthropod vector.

1. *Immunofluorescent Antibody Assay (IFA)*. Soon after the discovery of the etiologic agent of Lyme disease, IFA was developed to meet the demand for serological diagnosis. In this assay, microscope slides are coated with *B burgdorferi* obtained from cultures. Serial dilutions of serum obtained from patients suspected of having Lyme disease are then added to the slides, which are incubated, washed, and flooded with isothiocyanate anti-human immunoglobulin. Slides are incubated, washed, mounted, and examined using fluorescent microscopy.¹¹⁷ Several authorities agreed on 1:256 titer as a cutoff point for positive Lyme disease infection.²³

2. *Enzyme-Linked Immunosorbent Assay (ELISA)*. This serological tool is known for its accuracy. *Borrelia burgdorferi* extracts are used to coat the ELISA plates. A serial dilution of patient's serum is added to the wells, incubated and washed. P-nitrophenyl phosphate substrate is added, then washed, and the optical density measured spectrophotometrically at 405-410 nm. An optical density of >0.2 is considered positive.^{118, 119}

In serology, cross reactivity of serum coming from Lyme disease patients reacted strongly with other *Borrelia* antigens (*Borrelia hermsii*, the causative agent for tick-borne relapsing fever, and *Borrelia recurrentis*, the spirochete causing louse-borne relapsing fever). Antibodies directed against *Borrelia burgdorferi* reacted with *Treponema pallidum* when testing for syphilis.¹¹⁸ In addition, sera obtained from syphilitic patients cross reacted with both ELISA and IFA tests for Lyme disease. Moreover, cross reactivity was observed in cases of Rocky Mountain Spotted Fever (RMSF) and Lyme disease patients.

Culturing

The Lyme disease spirochete has been isolated from blood, cerebrospinal fluids, lesions, and synovial fluids from patients.¹¹⁷ *Borrelia* spirochetes multiply in BSK culture medium at 30-37°C. Growth does not occur at temperature higher than 40°C.¹²⁰

Detection of *B burgdorferi* in Ticks

Ticks collected from the field or attached to animals and man can be examined for the presence of *B burgdorferi*. Field-trapped mice are restrained in a wire-mesh cage over water. As the engorged ticks detach they will be collected from the water below and subsequently kept in a container at high relative humidity. After molting into the nymphal stage (about 30-35 days), they

are dissected and examined for the presence of spirochetes.

1. *Dark-field Microscopy*. The intestinal tract of the tick is rendered free and smeared on a microscope slide containing a drop of buffered potassium phosphate solution. A cover slip is applied and the preparation is examined under dark field to detect any viable spirochetes.

2. *Direct Immunofluorescent Antibody Assay (DFA)*. The ticks are treated as indicated above and the smear fixed with acetone. The slides may be stored under -70°C until examination. Fixed smears are placed in a humid chamber, flooded with isothiocyanate conjugate, incubated, and washed. Slides are mounted and examined using fluorescence microscopy (Figure 1).⁵⁷

3. *Culturing Tick Contents*. Flagged or attached *I dammini* ticks or both may be cultured to determine their infection with *Borrelia* spirochetes.

Homogenized tick extract may be cultured in Barbour-Stoerner-Kelly (BSK) medium, and the culture examined using dark field microscopy.

Discussion

Public awareness concerning the diagnosis, treatment, and epidemiology of Lyme disease has increased, along with the increase in the *I dammini* population and the rise in the incidence of the disease. More sophisticated laboratory techniques have made diagnosis more certain, and the public has been quick to learn that the tick they are observing is not always an American dog tick, but frequently the deer tick in one of its development stages. Advice from physicians, state and local health authorities, universities, and conservation groups has emphasized the need for quick and proper removal of the attached ticks. Perhaps more important, but not adequately appreciated by those who prefer to hike, play golf, and picnic in shorts, is the fact that the ticks can and should be prevented from reaching the skin in the first place. By wearing long pants tucked into the socks and long-sleeved shirts, many of the ticks can be physically prevented from reaching a suitable site for attachment. Proprietary preparations of tick repellents can also prevent most, if not all, of the ticks from gaining access. In any event, immediate checking for the presence of ticks upon return home and again a thorough inspection after showering should be routine. If ticks are attached, they should be carefully removed by grasping the specimen as close to the skin as possible and giving the tick a firm sustained pull. Obviously, it is much better to remove the attached tick before it has introduced

the spirochete than to treat the disease.

Areas regularly frequented by family members, such as back yards in suburban settings, may harbor an unexpectedly high population of *I. dammini*. As many as one tick per square meter have been reported in Westchester County, NY.²¹ In such instances chemical control may be seriously considered for reducing the vector population.

Much more remains to be learned about Lyme borreliosis. The ramifications of the disease are poorly understood, and the need for more study is imperative. The capacity of other ticks as well as other arthropods to transmit the disease is poorly defined, as is the role of various mammals and birds as reservoirs. Levels of spirochetemia in reservoir hosts and infectivity of vectors need to be accessed. The incidence of Lyme disease in the human population in any specific geographic area is often not known with any degree of accuracy, which may lead to unjustifiable epidemiological conclusions. Lyme borreliosis is probably much more prevalent than we have thought in the recent past.

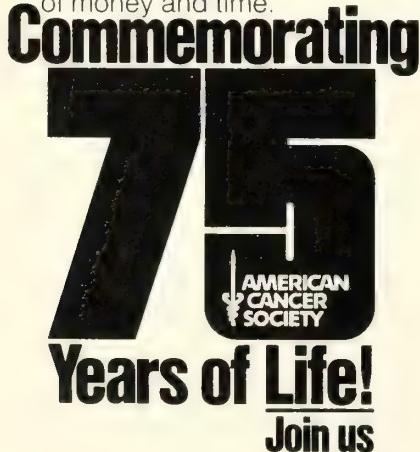
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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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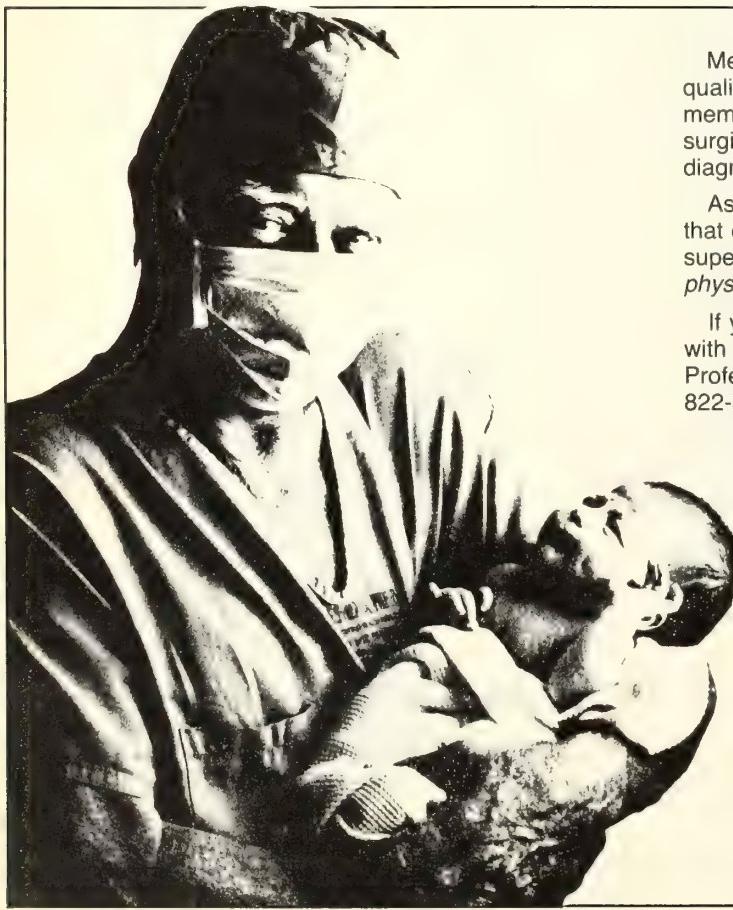
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Administer cautiously to allergic patients.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis.

Precautions:

- Discontinue Ceclor in the event of allergic reactions to it.
- Prolonged use may result in overgrowth of nonsusceptible organisms.
- Positive direct Coombs' tests have been reported during treatment with cephalosporins.
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in

moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.

- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include

- Gastrointestinal (mostly diarrhea): 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthritis; and frequently, fever]: 1.5%, usually subsides within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

● Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1%; and, rarely, thrombocytopenia.

Abnormalities in laboratory results of uncertain etiology

- Slight elevations in hepatic enzymes
- Transient fluctuations in leukocyte count (especially in infants and children)
- Abnormal urinalysis, elevations in BUN or serum creatinine
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Recent Abstracts of Interest

Gastrointestinal Tract and AIDS

A Practical Approach to Esophageal Problems in Acquired Immunodeficiency Disease (AIDS)

In AIDS patients odynophagia (pain on swallowing) or dysphagia (difficulty in food or liquid transfer from mouth to stomach) are frequent and difficult diagnostic or management problems. In AIDS, *Candida* esophagitis is the most common cause of esophageal symptoms. In this situation, patients with known oral candidiasis and esophageal symptoms, endoscopic esophagoscopy is diagnostic of associated esophageal *Candida* in almost all cases. Thus, appropriate antifungal therapy may be given without need for invasive endoscopic procedures in the presence of oral *Candida* infection with evaluation reserved for lack of resolution.

Other viruses such as Herpes simplex and cytomegalovirus (CMV) may cause ulcerating lesions of the esophagus, dysphagia or odynophagia which is the predominant clinical symptom of Herpes simplex infection. Rarely, oropharyngeal Kaposi's sarcoma or esophageal lymphoma may occur. *Cryptosporidium* may occasionally cause esophageal symptoms, though is much less common than involvement of the bowel or biliary tract. Diagnosis of esophageal complaints in AIDS patients is either by x-ray or endoscopy. X-ray has lower cost, less risk to patients and health care workers while endoscopy has greater sensitivity and ability to obtain material for culture, biopsy, and cytology. Many authorities recommend empiric therapeutic treatment of esophageal symptoms with antifungal agents such as ketoconazole since *Candida* is so common. Some success has been found in Herpes simplex and

CMV esophagitis with antiviral agents such as acyclovir and ganciclovir respectively. No current data strongly supports maintenance therapy to prevent recurrence or relapse.

Raufman, JP: Odynophagia/dysphagia in AIDS. *Gastro Clinics of NA*, 17:599, 1988.

A Comprehensive Review of Intestinal Infection in the "Gay Bowel Syndrome"

This report provides an excellent review of bowel disease in gay men and bowel complications of AIDS. Three hundred and eighty-eight homosexual men were studied to assess the spectrum of enteric pathogens in a population at high risk for the "gay bowel syndrome" in association with AIDS. Seventy-seven patients with AIDS, 68 gay men with acute diarrhea or symptoms of proctitis without AIDS, and 243 gay men without symptoms and without AIDS were studied. Twelve per cent of asymptomatic men harbored at least one potential enteric pathogen, especially *Chlamydia trachomatis*, Herpes simplex virus, and *Giardia lamblia*. Men with a pathogen were statistically more likely to be human immunodeficiency virus (HIV) seropositive, more likely to have fewer helper T cells, and more likely to have a mucopurulent exudate. In 68 per cent of AIDS patients with diarrhea or proctitis, an enteric pathogen was recovered (especially *Campylobacter* species, Herpes simplex virus, *Neisseria gonorrhoeae*, *Chlamydia*, *Giardia lamblia*, and *Shigella* species). Cryptosporidiosis was most common in

association with diarrhea in AIDS patients, found in 16 per cent of 49 cases. Approximately 50 per cent of the identified pathogens in AIDS patients with diarrhea were treatable with antibiotics, though specific culture techniques were needed.

Langhon BE et al: Prevalence of enteric pathogens in homosexual men with and without acquired immunodeficiency syndrome. *Gastroenterology* 94:984, 1988.

Multifactori Causes of Abnormal Liver Functions in AIDS

This is a salient review of liver and biliary disease in AIDS. Because of the epidemiologic similarities of hepatitis B virus (HBV) and HIV, markers of past HBV infection, namely anti HBs or anti HBe are found in up to 90 per cent of AIDS patients. Since the epidemiology of non-A, non-B hepatitis is similar, this is a common cause of liver dysfunction in AIDS, though a diagnosis of exclusion. Other infections, particularly *Mycobacterium avium intracellulare*, *Mycobacterium tuberculosis*, *Histoplasmosis*, CMV, and Cryptococcosis are also found on occasion. The liver in AIDS may also be involved with Kaposi's sarcoma which is rarely found antemortem as well as by malignant lymphoma which is typically a monoclonal B cell lymphoma. This review also discusses drug induced illness with a brief review of major potential hepatotoxins used in treatment of AIDS and its complications.

There is a discussion of indications for liver biopsy, opting for a conservative approach in reserving biopsy for AIDS patients with unexplained fever, chronic and major abnormalities of liver function tests in whom less invasive evaluation, such as biopsy of other sites and medication withdrawal, if practical, failed to yield a diagnosis. It is important to note that AIDS patients with cholestatic liver function results (ie, disproportionate abnormalities of the excretory enzymes, such as alkaline phosphatase and direct bilirubin) may have either an infectious form of hepatitis or biliary disease. In this context, patients with AIDS have been reported to have strictures of the bile duct, sclerosing cholangitis-like lesions, ampullary stenosis, and acalculous cholecystitis, all of which have been sometimes associated with either CMV or *Cryptosporidium* infection.

Lebovics E. et al: The hepato-biliary manifestations of HIV infection. *Am J Gastro* 83:1, 1988.

Acute Abdominal Pain in AIDS Has Varied and Unusual Etiologies

The charts of all AIDS patients requiring major surgery in a four year period at an urban university hospital were reviewed. Surgery performed for GI complications of AIDS included two cases of CMV perforation of ileum and colon, one case of bleeding ileo-colonic lymphoma and one case of *Cryptosporidium* acalculous cholecystitis. Laporotomy was performed in four patients for the diagnosis of retroperitoneal lymphadenopathy. Six patients underwent splenectomy for AIDS related immune thrombocytopenia. In this series 75 per cent of patients had pre-existing opportunistic infection or neoplasms unrelated to the acute surgical problem. This is a good review of HIV associated problems of the digestive tract. In particular, CMV may cause an acute abdominal crisis with colitis, ileitis, bowel perforation or acalculous cholecystitis. Both lymphoma and Kaposi's sarcoma have been reported in AIDS patients as a cause of bleeding from small or large bowel as well as being a potential cause of small bowel obstruction and perforation. In this series, postoperative complications in AIDS patients were common and consisted of wound infections, disseminated intravascular coagulation, small bowel obstruction, *Pneumocystis* pneumonia and CMV pneumonia.

Ferguson CM: Surgical complications of human immunodeficiency virus infection. *Amer Surg* 54:4, 1988.

Edited by Edward R. Feller, MD, Chairman, RIMJ Editorial Board

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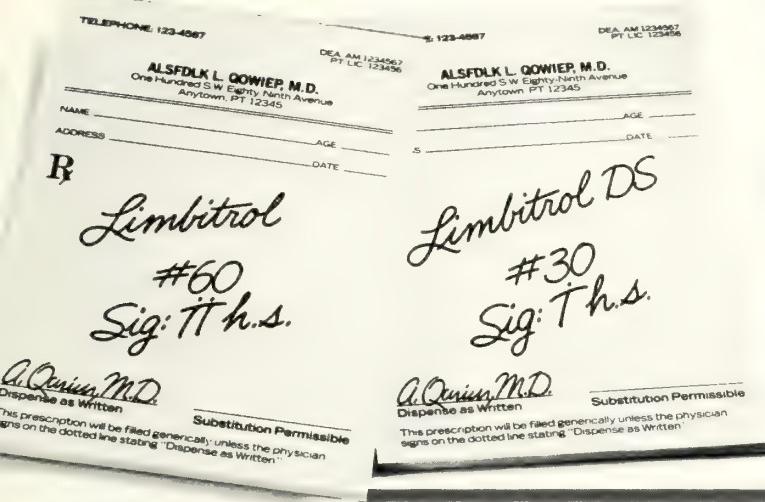
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Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

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Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

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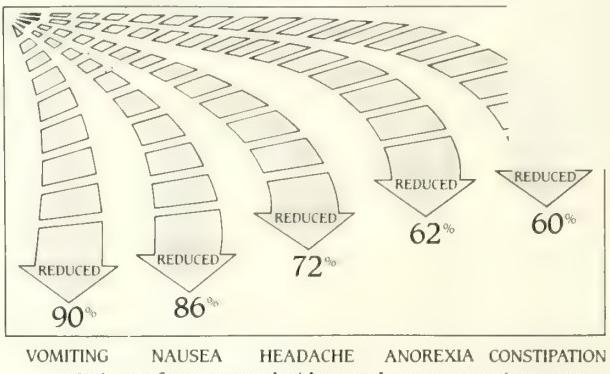
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